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(FILE 'HOME' ENTERED AT 14:07:47 ON 05 JUL 2005)
SET COST OFF

FILE 'HCAPLUS' ENTERED AT 14:07:56 ON 05 JUL 2005

E CHAPLIN D/AU
L1 364 S E3-E9,E11-E18
E YOUNG S/AU
L2 622 S E3-E30
E YOUNG SCOT/AU
L3 61 S E4-E14
E OXIGENE/PA,CS
L4 18 S E3-E10
L5 511 S ?COMBRETASTATIN?
L6 370 S ?COMBRETASTATIN? () (A1 OR A4 OR A 1 OR A 4)
L7 129 S L6 (L) ?PHOSPHATE?
L8 8 S L7 AND A1

FILE 'REGISTRY' ENTERED AT 14:12:12 ON 05 JUL 2005

L9 1 S 82855-09-2
L10 283 S C18H22O6/MF AND 46.150.18/RID AND 2/NR
L11 8 S L10 AND BENZENEETHANOL
L12 3 S L11 AND 3 4 5 TRIMETHOXYPHENYL
L13 2 S L12 NOT 4 HYDROXY
L14 5 S L10 AND COMBRETASTATIN
L15 5 S L9,L13,L14
L16 2 S 117048-59-6 OR 109971-63-3
L17 609 S C18H20O5/MF AND 46.150.18/RID AND 2/NR
L18 4 S L17 AND COMBRETASTATIN
L19 16 S L17 AND PHENOL AND ETHENYL
L20 3 S L19 AND 3 4 5 TRIMETHOXYPHENYL ETHENYL AND 2 METHOXY 5
L21 5 S L18,L20
L22 311 S C18H20O6/MF AND 46.150.18/RID AND 2/NR
L23 1 S L22 AND COMBRETASTATIN
L24 3 S L22 AND 1 2 BENZENEDIOL AND 3 4 5 TRIMETHOXYPHENYL ETHENYL AN
L25 2 S 222030-63-9 OR 288847-35-8
L26 5 S C18H21O8P/MF AND 46.150.18/RID AND 2/NR
L27 3 S L26 AND ETHENYL
L28 3 S C18H22O12P2/MF AND 46.150.18/RID AND 2/NR AND ETHENYL
L29 19 S L9,L15,L16,L21,L23,L24,L25,L27,L28
E COMBRETASTATIN
L30 33 S E3
L31 11 S L30 AND L29
L32 19 S L29,L31
L33 22 S L30 NOT L32
L34 41 S L32,L33
SEL RN
L35 51 S E1-E41/CRN
L36 25 S L35 AND (COMPD OR WITH OR MXS/CI)
L37 26 S L35 NOT L36
L38 64 S L34,L37

FILE 'HCAPLUS' ENTERED AT 14:23:14 ON 05 JUL 2005

L39 394 S L38
L40 511 S L5-L8
L41 52 S CA4P OR CA 4P
L42 540 S L39-L41
L43 1418 S PROPANOLOL
L44 9563 S (NA OR SODIUM) () (NITROPRUSSIDE OR NITRO PRUSSIDE)

FILE 'REGISTRY' ENTERED AT 14:25:34 ON 05 JUL 2005

L45 2 S 5051-22-9 OR 4199-09-1
E C16H21NO2/MF
L46 29 S E3 AND C6-C6/ES AND 2/NR AND 2 PROPANOL
L47 12 S L46 AND 3 1 NAPHTHALENYLOXY
L48 3 S L47 NOT (D/ELS OR 180 OR T/ELS OR 11C# OR 13C# OR LABELED)
L49 3 S E3 AND PROPANOLOL
L50 3 S L45,L48,L49
SEL RN
L51 121 S E1-E3/CRN
L52 17 S L51 NOT (MXS/CI OR COMPD OR WITH)
L53 16 S L52 NOT CONJUGATE
L54 19 S L50,L53
L55 1 S 14402-89-2
L56 1 S 15078-28-1
L57 480 S 15078-28-1/CRN
L58 30 S L57 AND NA/ELS
L59 5 S L58 AND 2/NC
SEL RN 4 5
L60 2 S E4-E5
L61 3 S L56,L60,L55

FILE 'HCAPLUS' ENTERED AT 14:30:02 ON 05 JUL 2005

L62 15018 S L54
L63 27374 S PROPANOLOL
L64 4507 S L61
L65 40302 S L43,L44,L62-L64
L66 6968 S BETA BLOCKER
E BETA BLOCKER/CT
E E4+ALL
E E2+ALL
L67 8368 S E7,E8,E6
L68 47959 S L65-L67
E ANTIHYPERTEN/CT
E E10+ALL
L69 26601 S E4
L70 72103 S L68,L69
L71 4 S L70 AND L42
L72 3 S L70 AND VASCULAR TARGET?
L73 7 S L71,L72
L74 1 S L1-L4 AND L73
E OXYGENE/PA,CS
L75 23 S E3-E8
L76 1 S L75 AND L73
L77 1 S L74,L76
L78 26 S L1-L4,L75 AND L42
L79 17 S L1-L4,L75 AND VASCULAR? (L) TARGET?
L80 28 S L78,L79
L81 1 S L80 AND L70
L82 7 S L73,L77,L81
L83 27 S L80 NOT L82
SEL DN AN 3 5 7
DEL SEL
SEL DN AN 3 5 7 L82
L84 3 S L82 AND E1-E9
L85 30 S L83,L84
L86 2 S L1 AND L2,L3
L87 9 S L1-L3 AND L4,L75
L88 10 S L86,L87

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L89      2 S L88 NOT L85
L90     22 S L85 AND (PY<=2002 OR PRY<=2002 OR AY<=2002)
L91      8 S L85 NOT L90
          SEL DN AN 7
L92      7 S L91 NOT E10-E12
L93     29 S L90,L92
          SEL RN

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FILE 'REGISTRY' ENTERED AT 14:40:25 ON 05 JUL 2005

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L94     334 S E13-E346
L95      1 S L94 AND L54,L61
L96     17 S L94 AND L38
L97    316 S L94 NOT L95,L96
L98     88 S L97 AND 46.150.18/RID AND NR>=2 AND ETHENYL
L99     29 S L98 AND NC>=2
L100    14 S L99 NOT (COMPD OR WITH OR MXS/CI)
L101    59 S L98 NOT L99

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=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 14:44:14 ON 05 JUL 2005

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FILE COVERS 1907 - 5 Jul 2005 VOL 143 ISS 2

FILE LAST UPDATED: 4 Jul 2005 (20050704/ED)

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This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d l93 all hitstr tot

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L93  ANSWER 1 OF 29  HCAPLUS  COPYRIGHT 2005 ACS on STN
AN   2004:942007  HCAPLUS
DN   142:253877
ED   Entered STN:  08 Nov 2004
TI   Phase I trial of the antivasular agent combretastatin
      A4 phosphate on a 5-day schedule to patients with
      cancer: magnetic resonance imaging evidence for altered tumor blood flow
AU   Stevenson, James P.; Rosen, Mark; Sun, Weijing; Gallagher, Maryann;
      Haller, Daniel G.; Vaughn, David; Giantonio, Bruce; Zimmer, Ross; Petros,
      William P.; Stratford, Michael; Chaplin, David; Young,
      Scott L.; Schnall, Mitchell; O'Dwyer, Peter J.
CS   University of Pennsylvania Cancer Center, Philadelphia, PA, USA
SO   Journal of Clinical Oncology (2003); 21(23), 4428-4438
      CODEN: JCONDN; ISSN: 0732-183X
PB   American Society of Clinical Oncology

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DT Journal
 LA English
 CC 1-6 (Pharmacology)
 AB Purpose: **Combretastatin A4 (CA4) phosphate (CA4P)** inhibits microtubule polymerization and is toxic to proliferating endothelial cells in vitro. It causes reversible vascular shutdown in established tumors in vivo, consistent with an antivascular mechanism of action. The present study investigated escalating doses of **CA4P** administered i.v. to patients with advanced cancer. Patients and Methods: Patients with solid malignancies and good performance status received **CA4P** as a 10-min infusion daily for 5 days repeated every 3 wk. Pharmacokinetic sampling was performed during cycle 1. Patients receiving ≥ 52 mg/m²/d had serial dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) studies to measure changes in tumor perfusion with **CA4P** treatment. Results: Thirty-seven patients received 133 treatment cycles. **CA4P** dose levels ranged from 6 mg/m² to 75 mg/m² daily. Severe pain at sites of known tumor was dose limiting at 75 mg/m². Dose-limiting cardiopulmonary toxicity (syncope and dyspnea or hypoxia) was noted as well in two patients treated at 75 mg/m². Other toxicities included hypotension, ataxia, dyspnea, nausea or vomiting, headache, and transient sensory neuropathy. Plasma **CA4P** and CA4 area under the concentration-time curve and maximal concentration values increased linearly with dose. Tumor perfusion, as measured by the first-order rate constant of gadolinium plasma to tissue transfer during DCE-MRI studies, was found to decrease in eight of 10 patients. Relationships were also demonstrated between perfusion changes and pharmacokinetic indexes. A partial response was observed in a patient with metastatic soft tissue sarcoma, and 14 patients exhibited disease stability for a min. of two cycles. Conclusion: Doses of **CA4P** on a daily times five schedule of 52 to 65 mg/m² were reasonably well-tolerated. The 52 mg/m² dose is recommended for further study based on cumulative phase 1 experience with **CA4P**. Antitumor efficacy was observed, and the use of DCE-MRI provided a valuable noninvasive measure of the vascular effects of **CA4P** treatment.

ST **combretastatin A4 phosphate** tumor
 circulation antivascular antitumor

IT Antitumor agents
 Human
 (altered tumor blood flow induced by antivascular agent
combretastatin A4 phosphate on a 5-day
 schedule to patients with cancer)

IT Blood vessel
 (endothelium; altered tumor blood flow induced by antivascular agent
combretastatin A4 phosphate on a 5-day
 schedule to patients with cancer)

IT Neoplasm
 (solid; altered tumor blood flow induced by antivascular agent
combretastatin A4 phosphate on a 5-day
 schedule to patients with cancer)

IT Endothelium
 (vascular; altered tumor blood flow induced by antivascular agent
combretastatin A4 phosphate on a 5-day
 schedule to patients with cancer)

IT 222030-63-9, **Combretastatin A4 phosphate**
 RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (altered tumor blood flow induced by antivascular agent

**combretastatin A4 phosphate on a 5-day
schedule to patients with cancer)**

RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE

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IT 222030-63-9, **Combretastatin A4
phosphate**

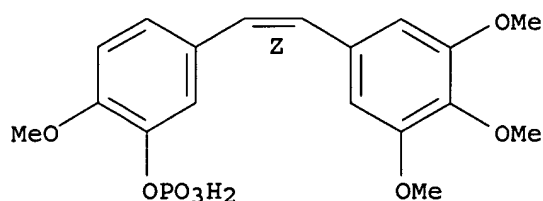
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(altered tumor blood flow induced by antivasular agent
**combretastatin A4 phosphate on a 5-day
schedule to patients with cancer)**

RN 222030-63-9 HCAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen phosphate (9CI) (CA INDEX NAME)

Double bond geometry as shown.



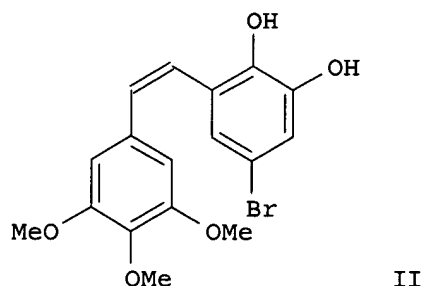
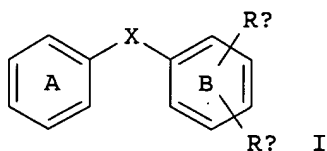
L93 ANSWER 2 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
 AN 2004:754412 HCAPLUS
 DN 141:277352
 ED Entered STN: 16 Sep 2004
 TI Preparation of quinone and catechol derivatives for the treatment of
 cancers and other vascular proliferative disorders
 IN **Chaplin, David J.**; Edvardsen, Klaus; Pinney, Kevin G.; Prezioso,
 Joseph Anthony; Wood, Mark
 PA **Oxigene, Inc., USA**
 SO PCT Int. Appl., 101 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 IC ICM A61K
 CC 25-16 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
 Section cross-reference(s): 1, 63

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004078126	A2	20040916	WO 2004-US6175	20040301
	W:				
	AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG,				
	BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR,				
	CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES,				
	ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN,				
	IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC,				
	LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX,				
	MZ, MZ, NA, NI				
	RW:				
	BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE,				
	BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU,				
	MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA,				
	GN, GQ, GW, ML, MR, NE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA,				
	GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2004242696	A1	20041202	US 2004-790662	20040301
PRAI	US 2003-450565P	P	20030228		
	US 2003-467486P	P	20030502		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004078126	ICM	A61K
US 2004242696	NCL	514/616.000; 514/720.000; 514/733.000; 514/649.000
OS	MARPAT 141:277352	
GI		



- AB The title compound I [Ring A is optionally substituted with one to five substituents selected from alkoxy, cycloalkoxy, halo, trihaloalkyl, alkyl, allyl, alc., (substituted)amino, oxo, alkanoyl, thiol, etc.; ring B comprises at lease one structure denoted by Ra and Rb which represent an ortho-quinone (-CO-CO-), or ortho-catechol (-COH-COH-) or ortho-catechol pro-drug moiety; the remaining carbons of B ring are optionally substituted with one to five substituents selected from alkoxy, cycloalkoxy, halo, trihaloalkyl, alkyl, allyl, alc., (substituted)amino, oxo, alkanoyl, thiol, etc.; Bridge X = alkene, alkane, alkyne, amide, amine, etc.] were prepared for the treatment of solid tumor cancers and other vascular proliferative disorders. For example, compound II was prepared in a multi-step synthesis starting from 5-bromo-2-hydroxy-3-methoxybenzaldehyde: The latter showed activity with IC50s of 2.1 and 0.34 μ M in the tubulin binding and MTT assays.
- ST quinone catechol deriv prepn cancer vascular proliferative disorder treatment
- IT Sarcoma
(Kaposi's; preparation of quinone and catechol derivs. for the treatment of cancers and other vascular proliferative disorders)
- IT Eye, disease
(diabetic retinopathy, treatment of; preparation of quinone and catechol derivs. for the treatment of cancers and other vascular proliferative disorders)
- IT Eye, disease
(macula, degeneration, treatment of; preparation of quinone and catechol derivs. for the treatment of cancers and other vascular proliferative disorders)
- IT Angiogenesis
(neovascularization, treatment of, corneal neovascularization; preparation of quinone and catechol derivs. for the treatment of cancers and other vascular proliferative disorders)
- IT Antitumor agents
Cytotoxic agents
Human
(preparation of quinone and catechol derivs. for the treatment of cancers and other vascular proliferative disorders)
- IT Artery, disease

(restenosis; preparation of quinone and catechol derivs. for the treatment of cancers and other vascular proliferative disorders)

IT Eye, disease
(retrolental fibroplasia, treatment of; preparation of quinone and catechol derivs. for the treatment of cancers and other vascular proliferative disorders)

IT Atherosclerosis
(treatment of, atheroma; preparation of quinone and catechol derivs. for the treatment of cancers and other vascular proliferative disorders)

IT Edema
(treatment of, diabetic mol. edema; preparation of quinone and catechol derivs. for the treatment of cancers and other vascular proliferative disorders)

IT Inflammation
Neoplasm
Psoriasis
Rheumatoid arthritis
(treatment of; preparation of quinone and catechol derivs. for the treatment of cancers and other vascular proliferative disorders)

IT Eye, disease
Inflammation
(uveitis, treatment of; preparation of quinone and catechol derivs. for the treatment of cancers and other vascular proliferative disorders)

IT 438534-69-1P 519060-17-4P 519060-18-5P 519060-19-6P 757996-09-1P
757996-10-4P 757996-11-5P 757996-12-6P 757996-13-7P 757996-14-8P
757996-15-9P 757996-16-0P 757996-17-1P 757996-18-2P 757996-19-3P
757996-20-6P 757996-21-7P 757996-22-8P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of quinone and catechol derivs. for the treatment of cancers and other vascular proliferative disorders)

IT 87-66-1, 1,2,3-Benzenetriol 90-00-6 98-80-6 100-39-0 101-02-0, Triphenylphosphite 106-95-6, reactions 122-51-0, Triethyl orthoformate 148-53-8, 3-Methoxysalicylaldehyde 363-52-0 1321-07-9, Iodoxybenzoic acid 2103-57-3 2144-08-3 4463-33-6 5034-74-2 20041-61-6 24677-78-9 61240-20-8 71295-21-1 **117048-59-6**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of quinone and catechol derivs. for the treatment of cancers and other vascular proliferative disorders)

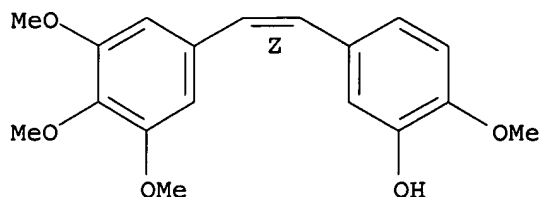
IT 86-51-1P 933-99-3P 1449-46-3P, Benzyltriphenylphosphonium bromide 4055-69-0P 6053-03-8P 52924-55-7P 58169-20-3P 64966-37-6P
73289-91-5P 103214-99-9P 109971-66-6P 132803-47-5P 132803-49-7P
144240-75-5P 183005-88-1P 757995-80-5P 757995-81-6P 757995-82-7P
757995-83-8P 757995-84-9P 757995-85-0P 757995-86-1P 757995-87-2P
757995-88-3P 757995-89-4P 757995-90-7P 757995-91-8P 757995-92-9P
757995-93-0P 757995-94-1P 757995-95-2P 757995-96-3P 757995-97-4P
757995-98-5P 757995-99-6P 757996-00-2P 757996-01-3P 757996-02-4P
757996-03-5P 757996-04-6P 757996-05-7P 757996-06-8P 757996-07-9P
757996-08-0P 757996-23-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of quinone and catechol derivs. for the treatment of cancers and other vascular proliferative disorders)

IT **117048-59-6**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of quinone and catechol derivs. for the treatment of cancers and other vascular proliferative disorders)

RN 117048-59-6 HCAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA

INDEX NAME)

Double bond geometry as shown.



L93 ANSWER 3 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
 AN 2004:690510 HCAPLUS
 DN 141:235461
 ED Entered STN: 24 Aug 2004
 TI **Combretastatin A4 phosphate**: background and current clinical status
 AU Young, Scott L.; Chaplin, David J.
 CS OXiGENE, Inc., Waltham, MA, 02451, USA
 SO Expert Opinion on Investigational Drugs (2004), 13(9), 1171-1182
 CODEN: EOIDER; ISSN: 1354-3784
 PB Ashley Publications Ltd.
 DT Journal; General Review
 LA English
 CC 1-0 (Pharmacology)
 AB A review. **Combretastatin A4 phosphate (CA4P)** represents the lead compound in a group of novel tubulin depolymerizing agents being developed as **vascular targeting** agents (VTAs). VTAs are drugs that induce rapid and selective **vascular dysfunction** in tumors. **CA4P** is a water-soluble prodrug of the cis-stilbene CA4 originally isolated from the tree *Combretum caffer*. Preclin. studies have shown that **CA4P** induces blood flow reductions and subsequent tumor cell death in a variety of preclin. models. Moreover, this activity has been linked to its ability to rapidly alter the morphology of immature endothelial cells by disrupting their tubulin cytoskeleton. Phase I clin. trials have established a maximum tolerated dose in the range 60-68 mg/m² and in addition have established that significant changes to tumor perfusion can be achieved across a wide range of doses. The dose-limiting toxicities include tumor pain, ataxia and cardiovascular changes. The maximum tolerated dose was independent of schedule, indicating the absence of cumulative toxicity. Although unexpected from preclin. studies, some evidence of clin. response was seen using **CA4P** as a single modality. Based on the Phase I data, combination studies of **CA4P** with established therapies are in progress and should determine whether the exciting preclin. data obtained when VTAs are used in combination with cytotoxic chemotherapy, radiation, radioimmunotherapy and even antiangiogenic agents, can be translated into man.
 ST review antitumor **combretastatin A4 phosphate**
 IT Antitumor agents
 Human
 Neoplasm
 (antitumor **combretastatin A4 phosphate**)
 IT 222030-63-9, **Combretastatin A4 phosphate**
 RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

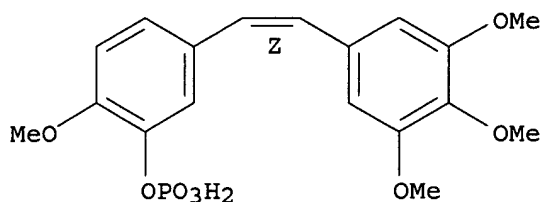
(antitumor combretastatin A4 phosphate)

RE.CNT 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE

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- (3) Bazett, H; Heart 1920, V7, P353
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 IT 222030-63-9, **Combretastatin A4 phosphate**
 RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (antitumor **combretastatin A4 phosphate**)
 RN 222030-63-9 HCAPLUS
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen phosphate (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L93 ANSWER 4 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
 AN 2004:653986 HCAPLUS
 DN 141:218487
 ED Entered STN: 13 Aug 2004
 TI **Combretastatin** family member OXI4503 induces tumor vascular collapse through the induction of endothelial apoptosis
 AU Sheng, Yezhou; Hua, Jianyi; Pinney, Kevin G.; Garner, Charles M.; Kane, Robert R.; Prezioso, Joseph A.; **Chaplin, David J.**; Edvardsen, Klaus
 CS Department of Cell and Molecular Biology, Section for Tumor Immunology, University of Lund, Lund, Swed.
 SO International Journal of Cancer (2004), 111(4), 604-610
 CODEN: IJCNW; ISSN: 0020-7136
 PB Wiley-Liss, Inc.
 DT Journal
 LA English
 CC 1-6 (Pharmacology)
 AB The mechanism of tumor cell killing by OXI4503 was investigated by studying **vascular** functional and morphol. changes post drug administration. SCID mice bearing MHEC5-T hemangioendothelioma were given a single dose of OXI4503 at 100 mg/kg. Tumor blood flow, measured by microsphere fluorescence, was reduced by 50% at 1 h, and reached a maximum level 6-24 h post drug treatment. Tumor **vascular** permeability, measured by Evan's blue and Hb, increased significantly from 3 h and peaked at 18 h. The elevated tumor vessel permeability was accompanied by an increase in **vascular** endothelial growth factor (VEGF) from 1 h post drug treatment. Immunohistochem. staining for CD31 and laminin showed that tumor blood vessels were affected as early as 3 h but more prominent from 6 h. From 12 h, the vessel structure was completely destroyed. Histopathol. and double immunohistochem. staining showed morphol. change and induction of apoptosis in endothelial cells at 1-3 h, followed by tumor cell necrosis from 6-72 h. There were no statistically significant changes of Evan's blue and Hb contents in liver tissue over the time course. These results suggest that OXI4503 selectively **targets** tumor blood vessels, and induces blood flow shutdown while it enhances tumor blood vessel permeability. The early induction of

endothelial cell apoptosis leads to functional changes of tumor blood vessels and finally to the collapse of tumor vasculature, resulting in massive tumor cell necrosis. The time course of the tumor **vascular** response observed with OXI4503 treatment supports this drug for development as a stand alone therapy, and also lends support for the use of the drug in combination with other cancer therapies.

- ST **combretastatin** blood vessel targeting permeability VEGF apoptosis
- IT CD antigens
 - RL: BSU (Biological study, unclassified); BIOL (Biological study) (CD31; in tumor vasculature after **combretastatin** family member OXI4503 administration in myocardial endothelioma cells)
- IT Cell adhesion molecules
 - RL: BSU (Biological study, unclassified); BIOL (Biological study) (PECAM-1 (platelet-endothelial cell adhesion mol. 1); in tumor vasculature after **combretastatin** family member OXI4503 administration in myocardial endothelioma cells)
- IT Antitumor agents
 - Apoptosis
 - Blood vessel
 - (**combretastatin** family member OXI4503 induces tumor vascular collapse through the induction of endothelial apoptosis)
- IT Blood vessel
 - (endothelium; **combretastatin** family member OXI4503 induces tumor vascular collapse through the induction of endothelial apoptosis)
- IT Laminins
 - RL: BSU (Biological study, unclassified); BIOL (Biological study) (in tumor vasculature after **combretastatin** family member OXI4503 administration in myocardial endothelioma cells)
- IT Blood vessel
 - (permeability; **combretastatin** family member OXI4503 induces tumor vascular collapse through the induction of endothelial apoptosis)
- IT Biological transport
 - (permeation, vascular; **combretastatin** family member OXI4503 induces tumor vascular collapse through the induction of endothelial apoptosis)
- IT Endothelium
 - (vascular; **combretastatin** family member OXI4503 induces tumor vascular collapse through the induction of endothelial apoptosis)
- IT 288847-35-8, Oxi 4503
 - RL: PAC (Pharmacological activity); BIOL (Biological study) (Oxi 4503; **combretastatin** family member OXI4503 induces tumor vascular collapse through the induction of endothelial apoptosis)
- IT 127464-60-2, Vascular endothelial growth factor
 - RL: BSU (Biological study, unclassified); BIOL (Biological study) (in tumor vasculature after **combretastatin** family member OXI4503 administration in myocardial endothelioma cells)

RE.CNT 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD
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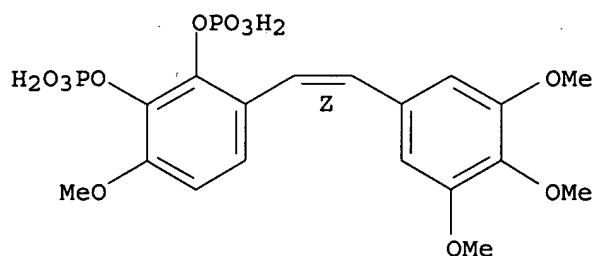
IT 288847-35-8, Oxi 4503

RL: PAC (Pharmacological activity); BIOL (Biological study)
 (Oxi 4503; **combretastatin** family member OXI4503 induces tumor
 vascular collapse through the induction of endothelial apoptosis)

RN 288847-35-8 HCAPLUS

CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-,
 bis(dihydrogen phosphate) (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L93 ANSWER 5 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2004:554208 HCAPLUS

DN 141:405555

ED Entered STN: 12 Jul 2004

TI **Vascular-targeting** therapies for treatment of malignant disease

AU Siemann, Dietmar W.; **Chaplin, David J.**; Horsman, Michael R.

CS Department of Radiation Oncology, University of Florida, Gainesville, FL, USA

SO Cancer (New York, NY, United States) (2004), 100(12), 2491-2499

CODEN: CANCAR; ISSN: 0008-543X

PB John Wiley & Sons, Inc.

DT Journal; General Review

LA English

CC 1-0 (Pharmacology)

AB A review. **BACKGROUND:** Tumor endothelium represents a valuable **target** for cancer therapy. The vasculature plays a critical role in the survival and continued growth of solid tumor masses; in addition, the inherent differences between tumor blood vessels and blood vessels associated with normal tissue make the tumor vasculature a unique **target** on which to base the design of novel therapeutics, which may allow highly selective treatment of malignant disease. Therapeutic strategies that **target** and disrupt the already formed vessel networks of growing tumors are actively being pursued. The goal of these approaches is to induce a rapid and catastrophic shutdown of the **vascular** function of the tumor so that blood flow is arrested and tumor cell death due to the resulting oxygen and nutrient deprivation and buildup of waste products occurs. **METHODS:** Biol. approaches and small-mol. drugs that can be used to damage tumor vasculature have been identified. **Physiol., histol./morphol., and immunohistochem. assessments** have demonstrated that profound disruption of the tumor vessel network can be observed minutes to hours after treatment. The small-mol. agents that, have made the greatest advances in the clin. setting (5,6-dimethylxanthenone-4-acetic acid [DMXAA], **combretastatin A4 disodium phosphate** [CA4DP], and ZD6126) are the focus of the current review. **RESULTS:** Loss of patent blood vessels, decreased tumor blood flow, extensive necrosis, and secondary ischemia-induced tumor cell death have been well documented in a variety of preclin. tumor models treated with agents such as DMXAA, CA4DP, and ZD6126. The use of such agents in conjunction with irradiation and other chemotherapeutic agents has led to improved treatment outcomes. **CONCLUSIONS:** The **targeting** of tumors' supportive blood vessel networks could lead to improvements in cancer cure rates. It is likely that this approach will prove to be most efficacious when used in concert with conventional treatment strategies.

ST review cancer blood vessel ZD6126 CA4DP DMXAA anticancer agent

IT Combination chemotherapy
(small-mol. agent with irradiation and chemotherapeutic agents improved

treatment outcome for malignant disease)

IT Neoplasm
(targeting of tumors supportive blood vessel networks by
5,6-dimethylxanthenone-4-acetic acid, **combretastatin**
A4 disodium **phosphate** and ZD6126 improved cancer cure
rate and shall be more effective when used with conventional treatment)

IT Antitumor agents
Blood vessel
(targeting of tumor's supportive blood vessel networks by
5,6-dimethylxanthenone-4-acetic acid, **combretastatin**
A4 disodium **phosphate** and ZD6126 improved cancer cure
rate and shall be more effective when used with conventional treatment)

IT Human
(targeting of tumor's supportive blood vessel networks by small-mol.
agent 5,6-dimethylxanthenone-4-acetic acid, **combretastatin**
A4 disodium **phosphate** and ZD6126 improved cancer
patient cure rate)

IT 117570-53-3, 5,6-Dimethylxanthenone-4-acetic acid
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(targeting of tumors by 5,6-dimethylxanthenone-4-acetic acid improved
cancer patient cure rate by loss of patent blood vessels, decreased
tumor blood flow, extensive necrosis and secondary ischemia-induced
tumor cell death)

IT 219923-05-4, ZD6126
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(targeting of tumors by ZD6126 improved cancer patient cure rate by
loss of patent blood vessels, decreased tumor blood flow, extensive
necrosis and secondary ischemia-induced tumor cell death)

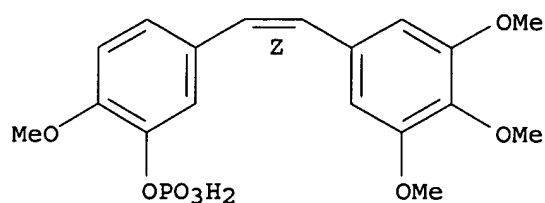
IT 168555-66-6, **Combretastatin A4** disodium
phosphate
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(targeting of tumors by **combretastatin A4** disodium
phosphate improved cancer patient cure rate by loss of patent
blood vessels, decreased tumor blood flow, extensive necrosis and
secondary ischemia-induced tumor cell death)

IT 168555-66-6, **Combretastatin A4** disodium
phosphate
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(targeting of tumors by **combretastatin A4** disodium
phosphate improved cancer patient cure rate by loss of patent
blood vessels, decreased tumor blood flow, extensive necrosis and
secondary ischemia-induced tumor cell death)

RN 168555-66-6 HCAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen
phosphate, disodium salt (9CI) (CA INDEX NAME)

Double bond geometry as shown.



● 2 Na

L93 ANSWER 6 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
 AN 2004:290417 HCAPLUS
 DN 140:281376
 ED Entered STN: 08 Apr 2004
 TI Method of administering split doses of a **vascular targeting agent**
 IN **Chaplin, David J.; Hill, Sally**
 PA UK
 SO U.S. Pat. Appl. Publ., 10 pp.
 CODEN: USXXCO
 DT Patent
 LA English
 IC ICM A61K031-075
 ICS A61K009-22
 INCL 424468000; 514720000
 CC 1-6 (Pharmacology)
 Section cross-reference(s): 63
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2004067255	A1	20040408	US 2002-265820	20021007 <--
PRAI	US 2002-265820		20021007	<--	

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 2004067255	ICM	A61K031-075
	ICS	A61K009-22
	INCL	424468000; 514720000
US 2004067255	NCL	424/468.000; 514/720.000
	ECLA	A61K031/075

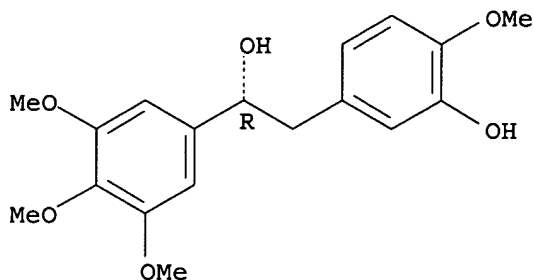
AB The present invention is directed to the use of **vascular targeting agents** or pharmaceutically acceptable salts thereof for administration in divided doses to a warm-blooded animal, such as a human. Also disclosed is a medicament comprising two or more fraction of doses of a **vascular targeting agent**, or a pharmaceutically acceptable salt thereof, which together add up to a total daily dose, or administration in divided doses for use in a method of treating a human or warm-blooded animal. A kit comprising two or more fractions of doses of a **vascular targeting agent** or a pharmaceutically acceptable salt thereof, which together add up to a total daily dose, for administration in divided doses is also disclosed.

ST **combretastatin split dose vascular targeting**
 antitumor

IT Animal
 (homiothermic; method of administering split doses of a

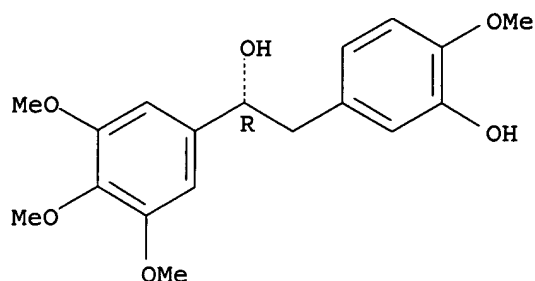
- vascular targeting agent)**
- IT Antitumor agents
Blood vessel, disease
Human
(method of administering split doses of a **vascular targeting agent**)
- IT Drug delivery systems
(prodrugs, phosphate; method of administering split doses of a **vascular targeting agent**)
- IT Drug delivery systems
(**vascular**; method of administering split doses of a **vascular targeting agent**)
- IT 82855-09-2, Combretastatin 82855-09-2D,
Combretastatin, analogs 117048-59-6D,
Combretastatin A-4, phosphate
prodrug salt of
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(method of administering split doses of a **vascular targeting agent**)
- IT 82855-09-2, Combretastatin 82855-09-2D,
Combretastatin, analogs 117048-59-6D,
Combretastatin A-4, phosphate
prodrug salt of
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(method of administering split doses of a **vascular targeting agent**)
- RN 82855-09-2 HCAPLUS
- CN Benzeneethanol, 3-hydroxy-4-methoxy- α -(3,4,5-trimethoxyphenyl)-,
(α R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



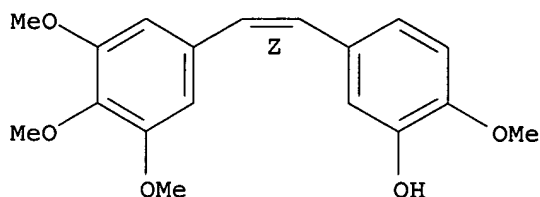
- RN 82855-09-2 HCAPLUS
- CN Benzeneethanol, 3-hydroxy-4-methoxy- α -(3,4,5-trimethoxyphenyl)-,
(α R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 117048-59-6 HCAPLUS
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L93 ANSWER 7 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
 AN 2003:535566 HCAPLUS
 DN 139:390868
 ED Entered STN: 14 Jul 2003
 TI Oxi4503, a novel **vascular targeting** agent: effects on blood flow and antitumor activity in comparison to **combretastatin A-4 phosphate**
 AU Hua, Jianyi; Sheng, Yezhou; Pinney, Kevin G.; Garner, Charles M.; Kane, Robert R.; Prezioso, Joseph A.; Pettit, George R.; **Chaplin, David J.**; Edvardsen, Klaus
 CS Department of Cell and Molecular Biology, Section for Tumor Immunology, University of Lund, Lund, 22184, Swed.
 SO Anticancer Research (2003), 23(2B), 1433-1440
 CODEN: ANTRD4; ISSN: 0250-7005
 PB International Institute of Anticancer Research
 DT Journal
 LA English
 CC 1-6 (Pharmacology)
 AB Oxi 4503, which is the **diphosphate** prodrug of **combretastatin A1**, is a novel **vascular targeting** agent from the **combretastatin** family. Another member of this family, **Combretastatin A-4 phosphate (CA4P)**, is a well-characterized **vascular targeting** agent already being evaluated in clin. trials. The potential for tumor **vascular targeting** by Oxi 4503 was assessed in a mouse system. This approach aims to shut down the established tumor vasculature, leading to the development of extensive tumor cell necrosis. The **vascular** effects of Oxi 4503 were assessed in the s.c. implanted MDAMB-231 adenocarcinoma and the MHEC5-T hemangioendothelioma in SCID mice and in a range of normal tissues. Blood flow was measured by i.v. injection of

fluorescence beads, while quant. fluorescence microscopy was used to measure the spatial heterogeneity of blood flow in tumor sections. Oxi 4503 induced the shutdown of tumor blood vessels in a dose-dependent pattern with an ED50 at 3 mg/kg in contrast to 43 mg/kg of **CA4P**. Quant. fluorescence microscopy showed that Oxi 4503 increased the spatial heterogeneity in tumor blood flow. Oxi 4503 affected peripheral tumor regions less than central regions, although this was not as pronounced as seen with **CA4P**, where only central regions were affected. The **vascular** shutdown induced by administration of Oxi 4503 at a dose of 6 mg/kg resulted in extensive cell loss 24 h following treatment, which translated into a significant effect on tumor growth. Tumor growth was completely repressed at doses above 12.5 mg/kg of Oxi 4503, while doses above 25 mg/kg showed tumor regression and even complete regression in some animals. These results are promising for the use of Oxi 4503 as a tumor **vascular targeting** agent. Moreover the potent antitumor effect when administered as a single agent suggests a different activity profile than **CA4P**.

ST Oxi4503 antitumor blood vessel targeting circulation
combretastatin A4 phosphate

IT Antitumor agents
Blood vessel, neoplasm
Circulation
Human

(Oxi 4503 effects on blood flow and antitumor activity in comparison to **combretastatin A-4 phosphate** in vascular tumors)

IT Drug delivery systems
(prodrugs; Oxi 4503 effects on blood flow and antitumor activity in comparison to **combretastatin A-4 phosphate** in vascular tumors)

IT 222030-63-9, **Combretastatin A-4 phosphate** 288847-35-8, Oxi 4503

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(Oxi 4503 effects on blood flow and antitumor activity in comparison to **combretastatin A-4 phosphate** in vascular tumors)

RE.CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE

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- (27) Murata, R; Int J Radiat Oncol Biol 2001, V51, P1018 HCAPLUS
- (28) Murata, R; Radiother Oncol 2001, V60, P155 HCAPLUS
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IT 222030-63-9, **Combretastatin A-4**

phosphate 288847-35-8, Oxi 4503

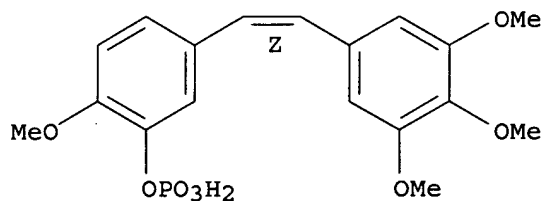
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)

(Oxi 4503 effects on blood flow and antitumor activity in comparison to
combretastatin A-4 phosphate in
vascular tumors)

RN 222030-63-9 HCAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen
phosphate (9CI) (CA INDEX NAME)

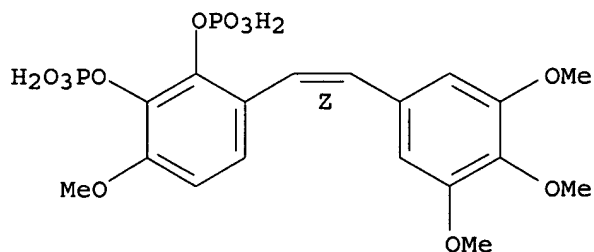
Double bond geometry as shown.



RN 288847-35-8 HCAPLUS

CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-,
bis(dihydrogen phosphate) (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L93 ANSWER 8 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2003:334852 HCAPLUS

DN 138:353746

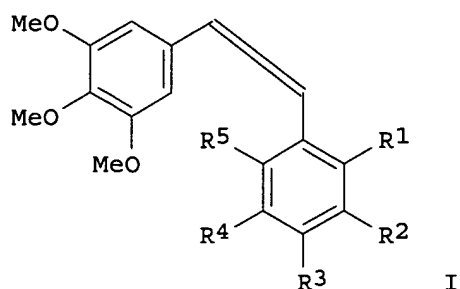
ED Entered STN: 02 May 2003
 TI Preparation of stilbenes as **vascular targeting agents**
 (VTAs) for treatment of solid tumors and retinal neovascularization.
 IN **Chaplin, David J.**; Garner, Charles Manly, III; Kane, Robert
 Ronald; Pinney, Kevin G.; Prezioso, Joseph Anthony
 PA **Oxigene, Inc., USA**; Evardsen, Klaus
 SO PCT Int. Appl., 56 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 IC ICM A61K
 CC 25-22 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
 Section cross-reference(s): 1

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003035008	A2	20030501	WO 2002-US34497	20021028 <--
	WO 2003035008	A3	20031113		
	W:				
	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,				
	CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,				
	GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,				
	LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,				
	PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,				
	UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
	RW:				
	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,				
	KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,				
	FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF,				
	CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2463902	AA	20030501	CA 2002-2463902	20021028 <--
	US 2003149003	A1	20030807	US 2002-281528	20021028 <--
	EP 1438281	A2	20040721	EP 2002-797056	20021028 <--
	R:				
	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				
	IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
	JP 2005507912	T2	20050324	JP 2003-537577	20021028 <--
PRAI	US 2001-337348P	P	20011026	<--	
	WO 2002-US34497	W	20021028	<--	

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2003035008	ICM	A61K
WO 2003035008	ECLA	C07C043/23; C07C045/63+47/575; C07C205/37; C07C207/04; C07C217/84; C07C237/04; C07F009/12+J <--
US 2003149003	NCL	514/130.000; 514/151.000; 514/567.000; 552/009.000; 558/190.000; 558/197.000; 562/434.000; 562/444.000; 564/305.000
	ECLA	C07C043/23; C07C045/63+47/575; C07C205/37; C07C207/04; C07C217/84; C07C237/04; C07F009/12+J <--
JP 2005507912	FTERM	4C086/AA01; 4C086/AA02; 4C086/DA34; 4C086/MA01; 4C086/MA04; 4C086/NA14; 4C086/ZA33; 4C086/ZA36; 4C086/ZB26; 4C086/ZB27; 4C086/ZC01; 4C206/AA01; 4C206/AA02; 4C206/GA18; 4C206/JA06; 4C206/MA01; 4C206/MA04; 4C206/NA14; 4C206/ZA33; 4C206/ZA36; 4C206/ZB26; 4C206/ZB27; 4C206/ZC01; 4H006/AA01; 4H006/AA03; 4H006/AB28; 4H006/BJ50; 4H006/BN10; 4H006/BP30; 4H006/BU32; 4H006/BV25; 4H006/GP03; 4H006/GP12; 4H006/GP22; 4H050/AA01; 4H050/AA03; 4H050/AB28 <--
OS	MARPAT 138:353746	
GI		



- AB Title compds. [I; R1, R4, R5 = H, OH, alkoxy, amino, NO₂, N₃, halo, phosphate ester salt; R2 = H, OH, alkoxy, amino, NO₂, amino, phosphate ester (salt); R1R2 = atoms to form a ring; R3 = H, alkoxy, phosphate ester salt], were prepared Thus, 3,4,5-trimethoxybenzyltriphenylphosphonium bromide (preparation given) in THF was treated with BuLi in THF at -15°; the mixture was stirred 30 min. at room temperature followed by addition of 2-(tert-butyldimethylsilyloxy)-3-bromo-4-methoxybenzaldehyde (preparation given) and stirring for 3h to give 78.7% E,Z-stilbene derivative, which was stirred with KF and HBr in DMF to give (Z)-2'-hydroxy-3'-bromo-3,4,4',5-tetramethoxystilbene. Tested I at 100 mg/kg i.p. in mice bearing MHEC-5T hemangioendothelioma tumors gave 41-90% blood flow shutdown.
- ST stilbene prepn **vascular targeting** agent tumor retinal neovascularization treatment; **combretastatin** analog prepn anticancer; diabetic retinopathy restenosis treatment stilbenoid analog prepn
- IT Nervous system, neoplasm
(central, treatment; preparation of stilbenes as **vascular targeting** agents (VTAs) for treatment of solid tumors and retinal neovascularization)
- IT Intestine, neoplasm
(colon, treatment; preparation of stilbenes as **vascular targeting** agents (VTAs) for treatment of solid tumors and retinal neovascularization)
- IT Artery, disease
(coronary, restenosis, treatment; preparation of stilbenes as **vascular targeting** agents (VTAs) for treatment of solid tumors and retinal neovascularization)
- IT Eye, disease
(diabetic retinopathy, treatment; preparation of stilbenes as **vascular targeting** agents (VTAs) for treatment of solid tumors and retinal neovascularization)
- IT Eye, disease
(macula, degeneration, treatment; preparation of stilbenes as **vascular targeting** agents (VTAs) for treatment of solid tumors and retinal neovascularization)
- IT Antitumor agents
Human
(preparation of stilbenes as **vascular targeting** agents (VTAs) for treatment of solid tumors and retinal neovascularization)
- IT Neoplasm
(solid, treatment; preparation of stilbenes as **vascular targeting** agents (VTAs) for treatment of solid tumors and retinal neovascularization)
- IT Kidney, neoplasm
Leukemia
Lung, neoplasm

Mammary gland, neoplasm
 Melanoma
 Ovary, neoplasm
 Prostate gland, neoplasm
 Thyroid gland, neoplasm
 (treatment; preparation of stilbenes as **vascular targeting** agents (VTAs) for treatment of solid tumors and retinal neovascularization)

IT Angiogenesis inhibitors
 (vascular targeting agents; preparation of stilbenes as **vascular targeting** agents (VTAs) for treatment of solid tumors and retinal neovascularization)

IT 519059-97-3P 519059-98-4P 519059-99-5P 519060-00-5P
 519060-01-6P 519060-02-7P 519060-46-9P
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (claimed compound; preparation of stilbenes as **vascular targeting** agents (VTAs) for treatment of solid tumors and retinal neovascularization)

IT 192710-93-3P 519060-03-8P 519060-04-9P 519060-05-0P 519060-06-1P
 519060-07-2P 519060-08-3P 519060-09-4P 519060-10-7P 519060-11-8P
 519060-12-9P 519060-13-0P 519060-14-1P 519060-15-2P 519060-16-3P
 519060-17-4P 519060-18-5P 519060-19-6P 519060-20-9P 519060-21-0P
 519060-22-1P 519060-23-2P 519060-24-3P 519060-25-4P
 519060-26-5P 519060-27-6P 519060-28-7P 519060-29-8P
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (preparation of stilbenes as **vascular targeting** agents (VTAs) for treatment of solid tumors and retinal neovascularization)

IT 519060-37-8 519060-38-9
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (preparation of stilbenes as **vascular targeting** agents (VTAs) for treatment of solid tumors and retinal neovascularization)

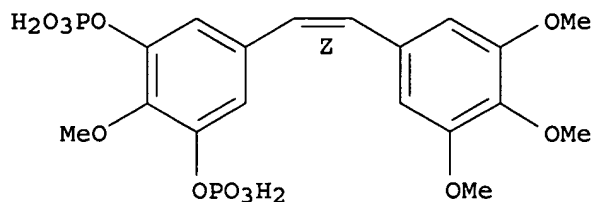
IT 673-22-3, 2-Hydroxy-4-methoxybenzaldehyde 3840-31-1,
 3,4,5-Trimethoxybenzyl alcohol 117048-59-6,
 Combretastatin A4 171778-08-8 519060-36-7
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (preparation of stilbenes as **vascular targeting** agents (VTAs) for treatment of solid tumors and retinal neovascularization)

IT 61240-20-8P, (3,4,5-Trimethoxybenzyl)triphenylphosphonium bromide
 63638-85-7P 519060-30-1P 519060-31-2P 519060-32-3P 519060-33-4P
 519060-34-5P 519060-35-6P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (preparation of stilbenes as **vascular targeting** agents (VTAs) for treatment of solid tumors and retinal neovascularization)

IT 519059-97-3P
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (claimed compound; preparation of stilbenes as **vascular targeting** agents (VTAs) for treatment of solid tumors and retinal neovascularization)

RN 519059-97-3 HCAPLUS
 CN 1,3-Benzenediol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, bis(dihydrogen phosphate), tetrasodium salt (9CI) (CA INDEX NAME)

Double bond geometry as shown.



●4 Na

IT 519060-22-1P

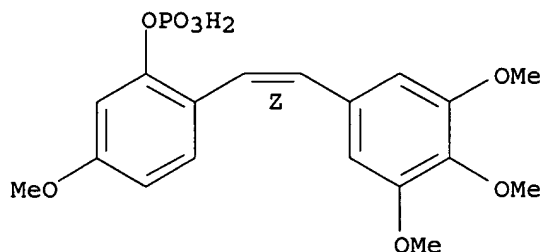
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of stilbenes as **vascular targeting agents** (VTAs) for treatment of solid tumors and retinal neovascularization)

RN 519060-22-1 HCAPLUS

CN Phenol, 5-methoxy-2-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen phosphate, disodium salt (9CI) (CA INDEX NAME)

Double bond geometry as shown.



●2 Na

IT 519060-38-9

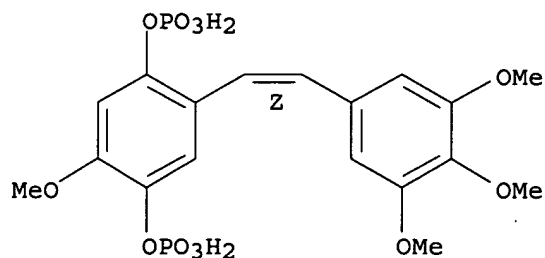
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(preparation of stilbenes as **vascular targeting agents** (VTAs) for treatment of solid tumors and retinal neovascularization)

RN 519060-38-9 HCAPLUS

CN 1,4-Benzenediol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, bis(dihydrogen phosphate), tetrasodium salt (9CI) (CA INDEX NAME)

Double bond geometry as shown.



●4 Na

IT 117048-59-6, Combretastatin A4

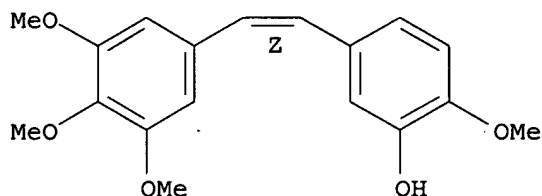
RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of stilbenes as **vascular targeting agents**
(VTAs) for treatment of solid tumors and retinal neovascularization)

RN 117048-59-6 HCAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA
INDEX NAME)

Double bond geometry as shown.



L93 ANSWER 9 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2003:202525 HCAPLUS

DN 138:243276

ED Entered STN: 14 Mar 2003

TI Vascular implants containing **combretastatin A-4** or **combretastatin A-4 phosphate**

IN Wnendt, Stephan; Chaplin, David; Kuttler, Bernd; Lorenz, Guenter

PA Oxygene Inc., USA

SO PCT Int. Appl., 61 pp.

CODEN: PIXXD2

DT Patent

LA German

IC ICM A61L033-16

ICS A61L029-16; A61L027-54

CC 63-6 (Pharmaceuticals)

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003020331	A1	20030313	WO 2002-EP9836	20020903 <--
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL,			

jan delaval - 5 july 2005

PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA,
 UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
 CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
 PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
 NE, SN, TD, TG

DE 10142897	A1	20030320	DE 2001-10142897	20010903 <--
DE 10142881	A1	20030403	DE 2001-10142881	20010903 <--
US 2005065595	A1	20050324	US 2004-488515	20041021 <--
PRAI DE 2001-10142881	A	20010903	<--	
DE 2001-10142897	A	20010903	<--	
WO 2002-EP9836	W	20020903	<--	

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES	
WO 2003020331	ICM	A61L033-16	
	ICS	A61L029-16; A61L027-54	
WO 2003020331	ECLA	A61L027/54; A61L029/16; A61L031/16	<--
DE 10142897	ECLA	A61L027/54; A61L029/16; A61L031/16	<--
DE 10142881	ECLA	A61L027/54; A61L029/16; A61L031/16	<--
US 2005065595	NCL	623/001.420; 623/001.440; 424/426.000; 427/002.250	
	ECLA	A61L027/54; A61L029/16; A61L031/16	<--

AB The invention relates to implants, in particular intracavernous or intravascular implants, preferably for the treatment or prophylaxis of coronary or peripheral vascular occlusion, strictures or stenosis, in particular for the prophylaxis of restenosis. The implants contain **combretastatin A-4** or **combretastatin A-4 phosphate** that is chemical bonded in a covalent or non-covalent form or is in a phys. fixed form. Stents prepared from alloys, polymers or their combination, also with alumina coating are treated with the alc. solution of **combretastatin A-4** or **combretastatin A-4 phosphate** under sterile condition. According to an other method **combretastatin A-4** or **combretastatin A-4 phosphate** are included in a biodegradable polymer for coating. Other drugs can be added to the implants.

ST vascular implant stent **combretastatin A4**

IT Platelet-derived growth factors
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (Antagonists; vascular implants containing **combretastatin A-4** or **combretastatin A-4 phosphate**)

IT Vascular endothelial growth factor receptors
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (activators of; vascular implants containing **combretastatin A-4** or **combretastatin A-4 phosphate**)

IT Prosthetic materials and Prosthetics
 (alloys, implants; vascular implants containing **combretastatin A-4** or **combretastatin A-4 phosphate**)

IT Angiotensin receptor antagonists
 (angiotensin II; vascular implants containing **combretastatin A-4** or **combretastatin A-4 phosphate**)

IT Prosthetic materials and Prosthetics
 (cardiovascular implants; vascular implants containing **combretastatin A-4** or **combretastatin A-4 phosphate**)

IT Medical goods

- (catheters; vascular implants containing **combretastatin A-4 or combretastatin A-4 phosphate**)
- IT Prosthetic materials and Prosthetics
(ceramics, ceramics coating; vascular implants containing **combretastatin A-4 or combretastatin A-4 phosphate**)
- IT Prosthetic materials and Prosthetics
(composites, implants; vascular implants containing **combretastatin A-4 or combretastatin A-4 phosphate**)
- IT Artery, disease
(coronary, restenosis; vascular implants containing **combretastatin A-4 or combretastatin A-4 phosphate**)
- IT Artery, disease
(coronary, stenosis; vascular implants containing **combretastatin A-4 or combretastatin A-4 phosphate**)
- IT Prosthetic materials and Prosthetics
(implants, intravascular; vascular implants containing **combretastatin A-4 or combretastatin A-4 phosphate**)
- IT Drug delivery systems
(implants; vascular implants containing **combretastatin A-4 or combretastatin A-4 phosphate**)
- IT Prosthetic materials and Prosthetics
(polymers; vascular implants containing **combretastatin A-4 or combretastatin A-4 phosphate**)
- IT Artery, disease
(restenosis; vascular implants containing **combretastatin A-4 or combretastatin A-4 phosphate**)
- IT Artery, disease
(stenosis; vascular implants containing **combretastatin A-4 or combretastatin A-4 phosphate**)
- IT Medical goods
(stents; vascular implants containing **combretastatin A-4 or combretastatin A-4 phosphate**)
- IT Drug delivery systems
(sustained-release; vascular implants containing **combretastatin A-4 or combretastatin A-4 phosphate**)
- IT Human
(vascular implants containing **combretastatin A-4 or combretastatin A-4 phosphate**)
- IT Fluoropolymers, biological studies
Polyester fibers, biological studies
Polyurethanes, biological studies
RL: DEV (Device component use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vascular implants containing **combretastatin A-4 or combretastatin A-4 phosphate**)
- IT Corticosteroids, biological studies

Interleukin 10

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (vascular implants containing **combretastatin A-4** or **combretastatin A-4 phosphate**)

- IT 329967-85-3, Cyclooxygenase 1
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (COX-1, inhibitors; vascular implants containing **combretastatin A-4** or **combretastatin A-4 phosphate**)
- IT 329900-75-6, COX-2
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (antagonists; vascular implants containing **combretastatin A-4** or **combretastatin A-4 phosphate**)
- IT 1344-28-1, Alumina, biological studies
 RL: DEV (Device component use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (coating for implants; vascular implants containing **combretastatin A-4** or **combretastatin A-4 phosphate**)
- IT 10102-43-9, Nitric oxide, biological studies
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (donors; vascular implants containing **combretastatin A-4** or **combretastatin A-4 phosphate**)
- IT 9002-04-4, Thrombin 9015-82-1, Angiotensin-converting enzyme
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (inhibitors; vascular implants containing **combretastatin A-4** or **combretastatin A-4 phosphate**)
- IT 9054-75-5, Guanylate-Cyclase
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (soluble, stimulants of; vascular implants containing **combretastatin A-4** or **combretastatin A-4 phosphate**)
- IT 9002-84-0, PTFE 25087-26-7, Methacrylic acid homopolymer
 RL: DEV (Device component use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (vascular implants containing **combretastatin A-4** or **combretastatin A-4 phosphate**)
- IT 50-02-2, Dexamethasone 50-28-2, 17 β -Estradiol, biological studies
 50-76-0, Actinomycin D 52-53-9, Verapamil 53-03-2, Prednisone
 53-86-1, Indomethacin 55-63-0, Nitroglycerin 59-05-2, Methotrexate
 64-17-5, Ethanol, biological studies 67-56-1, Methanol, biological studies
 86-54-4, Hydralazin 378-44-9, Betamethasone 865-21-4, Vinblastin
 8001-27-2, Hirudin 14402-89-2, **Sodium nitroprusside** 15307-86-5, Diclofenac 15663-27-1, Cisplatin
 15687-27-1, Ibuprofen 21829-25-4, Nifedipine 22204-53-1, Naproxen
 23288-49-5, Probucol 24280-93-1, Mycophenolic acid 25717-80-0, Molsidomine
 33069-62-4, Paclitaxel 33876-97-0, Linsidomine 42399-41-7, Diltiazem
 53123-88-9, Rapamycin 53902-12-8, Tranilast 62571-86-2, Captopril
 65271-80-9, Mitoxantrone 66085-59-4, Nimodipine 71125-38-7, Meloxicam
 71142-71-7, PPACK 75847-73-3, Enalapril 76547-98-3, Lisinopril
 79217-60-0, Cyclosporin 85441-61-8, Quinapril 104987-11-3, FK506
 114798-26-4, Losartan 117048-59-6, **Combretastatin A-4** 123948-87-8, Topotecan
 127464-60-2, Vascular endothelial growth factor 128270-60-0, Hirulog
 137862-53-4, Valsartan 138402-11-6, Irbesartan 139481-59-7,

Candesartan 140208-23-7, Plasminogen activator inhibitor I
 143653-53-6, Rheopro 146426-40-6, Flavopiridol 159351-69-6, SDZ RAD
 162011-90-7, Vioxx 169590-42-5, Celebrex 185681-64-5, 7-Hexanoyl-Taxol
 222030-63-9, Combretastatin A-4

phosphate 256376-24-6, BAY 41-2272

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (vascular implants containing **combretastatin A-4**
4 or combretastatin A-4
phosphate)

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
 RE

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- (2) Oxigene Inc; WO 0048606 A 2000 HCAPLUS
- (3) Schierholz Joerg Michael Dr Dr; EP 0985413 A 2000 HCAPLUS
- (4) Von Oepen, R; WO 02065947 A 2002

IT 14402-89-2, Sodium nitroprusside

117048-59-6, Combretastatin A-4

222030-63-9, Combretastatin A-4

phosphate

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

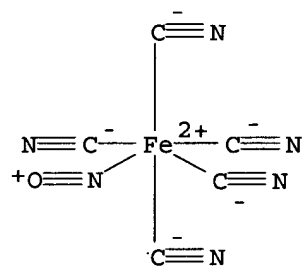
(vascular implants containing **combretastatin A-**

4 or combretastatin A-4

phosphate)

RN 14402-89-2 HCAPLUS

CN Ferrate(2-), pentakis(cyano-κC)nitrosyl-, disodium, (OC-6-22) - (9CI)
 (CA INDEX NAME)

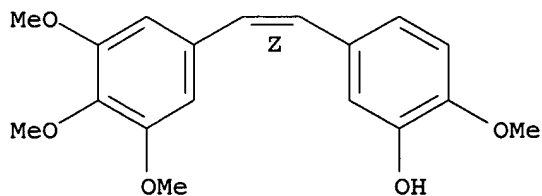


● 2 Na⁺

RN 117048-59-6 HCAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl] - (9CI) (CA
 INDEX NAME)

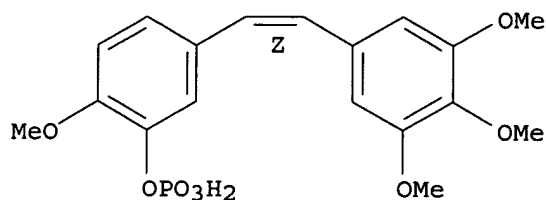
Double bond geometry as shown.



RN 222030-63-9 HCAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen phosphate (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L93 ANSWER 10 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
 AN 2003:162368 HCAPLUS
 ED Entered STN: 04 Mar 2003
 TI The First International Conference on **Vascular Targeting**
 : Meeting Overview
 AU Thorpe, Philip E.; **Chaplin, David J.**; Blakey, David C.
 CS Department of Pharmacology and Simmons Cancer Center, University of Texas
 Southwestern Medical Center, Dallas, TX, 75390, USA
 SO Cancer Research (2003), 63(5), 1144-1147
 CODEN: CNREA8; ISSN: 0008-5472
 PB American Association for Cancer Research
 DT Journal
 LA English
 AB The First International Conference on **Vascular Targeting**
 focused on **vascular targeting** agents (VTAs) that
 occlude or destroy the pre-existing blood vessels of solid tumors. The
 VTAs cause a rapid shutdown in the blood supply to the tumor that kills
 tumor cells by depriving them of oxygen and nutrients. The VTAs are
 distinct from antiangiogenic agents, which prevent new blood vessel
 formation. Two major types of VTAs are being developed for cancer: the
 ligand-directed VTAs that use antibodies, peptides, and growth factors to
 deliver toxins, procoagulants, and proapoptotic effectors to tumor
 endothelium, and the small mol. VTAs that do not specifically localize to
 tumor endothelium but exploit pathophysiol. differences between tumor and
 normal tissue endothelia to induce acute **vascular** shutdown in
 tumors. Both approaches were described at the meeting and highlighted the
 variety of VTAs in preclin. development, their selectivity for tumor
 endothelium, their rapid antitumor effects, and the improved activity seen
 when combined with other anticancer approaches (antiproliferative
 chemotherapeutic drugs, radiation, radiolabeled antibodies, nitric oxide
 synthetase inhibitors, and antiangiogenic agents). Early clin. studies
 were summarized for the small mol. VTAs: the antitubulin drugs,
combretastatin A4 phosphate (CA4P)
 and ZD6126, and the flavonoid, 5,6-dimethylxanthene-4-acetic acid
 (DMXAA). The agents lacked the bone marrow and gastrointestinal
 toxicities associated with antiproliferative chemotherapy. As a marker of
 biol. effect, blood flow redns. in tumors were measured using magnetic
 resonance imaging or positron emission tomog. for all of the agents
 tested, and single-agent clin. activity was seen. These agents are now
 being evaluated in combined modality studies to see whether the impressive
 results obtained in exptl. models can be translated into humans.
 RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
 RE
 (1) Blakey, D; Clin Cancer Res 2002, V8, P1974 HCAPLUS
 (2) Burrows, F; Pharmacol Ther 1994, V64, P155 HCAPLUS

- (3) Burrows, F; Proc Natl Acad Sci USA 1993, V90, P8996 HCAPLUS
- (4) Chaplin, D; Radiother Oncol 1994, V3, P59
- (5) Ching, L; Cancer Res 1999, V59, P3304 HCAPLUS
- (6) Denekamp, J; Br J Radiol 1993, V66, P181 MEDLINE
- (7) Denekamp, J; Cancer Metastasis Rev 1990, V9, P267 MEDLINE
- (8) Griggs, J; Am J Pathol 2002, V160, P1097 HCAPLUS
- (9) Hill, S; Eur J Cancer 1993, V29A, P1320 HCAPLUS
- (10) Huang, X; Science (Wash DC) 1997, V275, P547 HCAPLUS
- (11) Pedley, R; Cancer Res 2001, V61, P4716 HCAPLUS
- (12) Siemann, D; Int J Radiat Oncol Biol Phys 2002, V53, P164 HCAPLUS
- (13) Tozer, G; Int J Exp Pathol 2002, V83, P21 HCAPLUS

L93 ANSWER 11 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:149007 HCAPLUS
DN 139:239366
ED Entered STN: 27 Feb 2003
TI Selective induction of tumor ischemia: development of **vascular targeting** agents for cancer therapy
AU Chaplin, David J.; Hill, Sally A.
CS OXIGENE Inc, Watertown, MA, 02472, USA
SO Current Opinion in Investigational Drugs (PharmaPress Ltd.) (2002), 3(9), 1381-1384
CODEN: COIDAZ; ISSN: 1472-4472
PB PharmaPress Ltd.
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
AB A review of **vascular targeting** agents (VTAs) and the rationale for their use as anticancer agents. These compds. include flavanoids, ligand **targeted**, and tubulin depolymg. agents. Activity of VTAs in exptl. tumor models and clin. evaluations is also discussed.
ST review **vascular targeting** agent antitumor tumor ischemia cancer
IT Antitumor agents
Drug **targets**
Human
(developing **vascular targeting** agents for selective induction of tumor ischemia)
IT Blood vessel
(endothelium; developing **vascular targeting** agents for selective induction of tumor ischemia)
IT Neoplasm
(ischemia; developing **vascular targeting** agents for selective induction of tumor ischemia)
IT Ischemia
(tumor; developing **vascular targeting** agents for selective induction of tumor ischemia)
IT Endothelium
(**vascular**; developing **vascular targeting** agents for selective induction of tumor ischemia)

L93 ANSWER 12 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:57889 HCAPLUS
DN 138:112414
ED Entered STN: 24 Jan 2003
TI Compositions and methods of administering tubulin-binding agents for the treatment of ocular diseases
IN Sherris, David; Wood, Mark
PA Oxigene, Inc., USA

SO PCT Int. Appl., 59 pp.
CODEN: PIXXD2

DT Patent

LA English

IC A61K031-135

CC 63-5 (Pharmaceuticals)

Section cross-reference(s): 1

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003006002	A1	20030123	WO 2002-US22449	20020715 <--
	WO 2003006002	C1	20040527		
	WO 2003006002	C2	20040722		
	W:				
	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,				
	CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,				
	GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,				
	LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,				
	PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,				
	UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
	RW:				
	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,				
	KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,				
	FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF,				
	CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2453442	AA	20030123	CA 2002-2453442	20020715 <--
	EP 1406600	A1	20040414	EP 2002-756487	20020715 <--
	R:				
	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				
	IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
	JP 2004536847	T2	20041209	JP 2003-511808	20020715 <--
	US 2003181531	A1	20030925	US 2003-344886	20030211 <--
	US 2004229960	A1	20041118	US 2003-732680	20031209 <--
PRAI	US 2001-386227P	P	20010713	<--	
	US 2002-377556P	P	20020502	<--	
	US 2002-377845P	P	20020503	<--	
	US 2002-377847P	P	20020503	<--	
	WO 2002-US22449	W	20020715	<--	
	US 2003-344886	A2	20030211		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2003006002	IC	A61K031-135
WO 2003006002	ECLA	A61K031/135
JP 2004536847	FTERM	4C076/AA09; 4C076/AA12; 4C076/BB11; 4C076/BB24; 4C076/CC10; 4C076/CC11; 4C076/CC27; 4C076/CC42; 4C076/FF11; 4C084/AA17; 4C084/MA17; 4C084/MA28; 4C084/MA58; 4C084/MA66; 4C084/NA14; 4C084/NA15; 4C084/ZA33; 4C084/ZA36; 4C084/ZB26; 4C084/ZC41; 4C206/AA01; 4C206/AA02; 4C206/CA34; 4C206/MA01; 4C206/MA04; 4C206/MA37; 4C206/MA48; 4C206/MA78; 4C206/MA86; 4C206/NA14; 4C206/ZA33; 4C206/ZA36; 4C206/ZB26; 4C206/ZC41
US 2003181531	NCL	514/720.000
	ECLA	A61K031/00+A; A61K031/09
US 2004229960	NCL	514/720.000
	ECLA	A61K031/00+A; A61K031/09; A61K031/135

AB The present invention is directed to the administration of
vascular targeting agents, particularly a
tubulin-binding agent, for the treatment of ocular neovascularization,
ocular tumors, and conditions such as diabetic retinopathy, retinopathy of
prematurity, retinoblastoma and macular degeneration.

ST tubulin modulator eye neovascularization

IT Tubulins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(-binding agents; compns. and methods of administering tubulin-binding agents for the treatment of ocular diseases)

IT Drug delivery systems
(carriers; compns. and methods of administering tubulin-binding agents for the treatment of ocular diseases)

IT Eye
(choroid, neovascularization; compns. and methods of administering tubulin-binding agents for the treatment of ocular diseases)

IT Eye, neoplasm
(choroidal melanoma; compns. and methods of administering tubulin-binding agents for the treatment of ocular diseases)

IT Eye, disease
Iontophoresis
(compns. and methods of administering tubulin-binding agents for the treatment of ocular diseases)

IT Eye
(cornea, neovascularization; compns. and methods of administering tubulin-binding agents for the treatment of ocular diseases)

IT Eye, disease
(diabetic retinopathy; compns. and methods of administering tubulin-binding agents for the treatment of ocular diseases)

IT Drug delivery systems
(injections; compns. and methods of administering tubulin-binding agents for the treatment of ocular diseases)

IT Melanoma
(intraocular; compns. and methods of administering tubulin-binding agents for the treatment of ocular diseases)

IT Eye, disease
(macula, degeneration; compns. and methods of administering tubulin-binding agents for the treatment of ocular diseases)

IT Angiogenesis
(neovascularization, retinal; compns. and methods of administering tubulin-binding agents for the treatment of ocular diseases)

IT Eye, neoplasm
(neovascularization; compns. and methods of administering tubulin-binding agents for the treatment of ocular diseases)

IT Drug delivery systems
(ophthalmic; compns. and methods of administering tubulin-binding agents for the treatment of ocular diseases)

IT Eye, neoplasm
(primary ocular lymphoma; compns. and methods of administering tubulin-binding agents for the treatment of ocular diseases)

IT Drug delivery systems
(prodrugs, for **combretastatin A4**; compns. and methods of administering tubulin-binding agents for the treatment of ocular diseases)

IT Eye, disease
(retina, neovascularization; compns. and methods of administering tubulin-binding agents for the treatment of ocular diseases)

IT Eye, neoplasm
(retinoblastoma; compns. and methods of administering tubulin-binding agents for the treatment of ocular diseases)

IT Eye, disease
(retrolental fibroplasia; compns. and methods of administering tubulin-binding agents for the treatment of ocular diseases)

IT Drug delivery systems
(solns., ophthalmic; compns. and methods of administering tubulin-binding agents for the treatment of ocular diseases)

IT Drug delivery systems
(systemic; compns. and methods of administering tubulin-binding agents
for the treatment of ocular diseases)

IT 7647-14-5, Sodium chloride, biological studies 9004-32-4,
Carboxymethylcellulose
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(compns. and methods of administering tubulin-binding agents for the
treatment of ocular diseases)

IT 117048-59-6, Combretastatin A4
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(compns. and methods of administering tubulin-binding agents for the
treatment of ocular diseases)

RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD

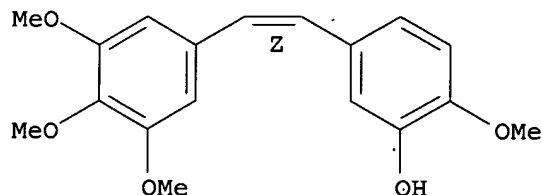
RE
(1) D'Amato; US 5504074 A 1996 HCAPLUS

IT 117048-59-6, Combretastatin A4
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(compns. and methods of administering tubulin-binding agents for the
treatment of ocular diseases)

RN 117048-59-6 HCAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA
INDEX NAME)

Double bond geometry as shown.



L93 ANSWER 13 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2003:10896 HCAPLUS

DN 139:46518

ED Entered STN: 07 Jan 2003

TI ZD6126: a novel **vascular-targeting** agent that causes
selective destruction of tumor vasculature

AU Davis, Peter D.; Dougherty, Graeme J.; Blakey, David C.; Galbraith, Susan
M.; Tozer, Gillian M.; Holder, Angela L.; Naylor, Matthew A.; Nolan, John;
Stratford, Michael R. L.; **Chaplin, David J.**; Hill, Sally A.

CS Oxford Science Park, Angiogene Pharmaceuticals Ltd., Oxford, OX4 4GA, UK

SO Cancer Research (2002), 62(24), 7247-7253
CODEN: CNREA8; ISSN: 0008-5472

PB American Association for Cancer Research

DT Journal

LA English

CC 1-6 (Pharmacology)

AB Physiol. differences between tumor and normal vasculature provide a
target for drug discovery. In particular, the immature nature of
tumor vasculature may render it intrinsically sensitive to disruption by
agents affecting the endothelial cell cytoskeleton, including
tubulin-binding agents. In this article, we report the synthesis of a
water-soluble phosphate prodrug, ZD6126, of the tubulin-binding agent

N-acetylcolchicinol. In vitro studies demonstrate the comparative tubulin-binding properties of the prodrug and active drug, and show the induction of pronounced, reversible changes in endothelial cell morphol. at subcytotoxic doses. Neither ZD6126 nor N-acetylcolchicinol showed effects on the growth of human umbilical vein endothelial cells at concns. below 100 μ M. In contrast, changes in endothelial cell morphol. were seen at much lower, noncytotoxic concns. (0.1 μ M) of ZD6126 and more pronounced effects were seen in proliferating vs. confluent endothelial cell cultures. In vivo studies were carried out using a murine tumor model (CaNT) with single administration of a dose well below the maximum tolerated dose. These studies showed a large reduction in **vascular** volume, induction of extensive necrosis in tumors, and a reduced tumor cell yield in a clonal excision assay, consistent with **vascular** rather than cytotoxic effects. A viable rim of tumor remained after single-dose administration and minimal growth delay was observed. However, well-tolerated, multiple administration regimens led to pronounced tumor-growth delay. In the human xenograft FaDu, the growth delay given by a single dose of paclitaxel was enhanced by combination with a single dose of ZD6126, and the growth delay given by the combination was greater than the sum of the growth delays from the individual treatments. These findings show that ZD6126 is a promising antivascular agent for the treatment of solid tumors.

- ST ZD6126 prepn acetylcolchicinol antiangiogenic antitumor mammary adenocarcinoma
- IT Angiogenesis inhibitors
Antitumor agents
Human
(ZD6126, a novel **vascular-targeting** agent that causes selective destruction of tumor vasculature)
- IT Mammary gland, neoplasm
(adenocarcinoma; ZD6126, a novel **vascular-targeting** agent that causes selective destruction of tumor vasculature)
- IT Carcinoma
(mammary adenocarcinoma; ZD6126, a novel **vascular-targeting** agent that causes selective destruction of tumor vasculature)
- IT Drug interactions
(synergistic; ZD6126, a novel **vascular-targeting** agent that causes selective destruction of tumor vasculature)
- IT 219923-05-4P, ZD6126
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(ZD6126, a novel **vascular-targeting** agent that causes selective destruction of tumor vasculature)
- IT 38838-26-5, N-Acetylcolchicinol
RL: PAC (Pharmacological activity); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(ZD6126, a novel **vascular-targeting** agent that causes selective destruction of tumor vasculature)
- IT 33069-62-4, Paclitaxel
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ZD6126, a novel **vascular-targeting** agent that causes selective destruction of tumor vasculature)
- IT 64-86-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(ZD6126, a novel **vascular-targeting** agent that causes selective destruction of tumor vasculature)
- IT 477-27-0P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(ZD6126, a novel **vascular-targeting** agent that causes selective destruction of tumor vasculature)

RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

- (1) Anon; Br J Cancer 1998, V77, P1
- (2) Baguley, B; Eur J Cancer 1991, V27, P482 HCAPLUS
- (3) Berenstein, A; Am J Neuroradiol 1981, V2, P261 MEDLINE
- (4) Boucher, Y; Cancer Res 1990, V50, P4478 MEDLINE
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- (6) Cech, J; Collect Czech Chem Commun 1949, V4, P532
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- (10) Dark, G; Cancer Res 1997, V57, P1829 HCAPLUS
- (11) Denekamp, J; Cancer Metastasis Rev 1990, V9, P267 MEDLINE
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- (13) Folkman, J; Nat Med 1995, V1, P27 HCAPLUS
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- (17) Hill, S; Eur J Cancer Clin Oncol 1989, V25, P1419 HCAPLUS
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- (19) Kang, G; J Biol Chem 1990, V265, P10255 HCAPLUS
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- (22) O'Reilly, M; Nat Med 1996, V2, P689 HCAPLUS
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- (24) Sabouraud, A; Z Gastroenterol 1992, V30(Suppl), P35
- (25) Strawn, L; Cancer Res 1996, V56, P3540 HCAPLUS
- (26) Takeguchi, K; Exp Cell Res 1990, V186, P374
- (27) Tozer, G; Cancer Res 1999, V59, P1626 HCAPLUS
- (28) Tozer, G; Cancer Res 2001, V61, P6413 HCAPLUS
- (29) van Tellingen, O; Anticancer Res 1992, V12, P1699 HCAPLUS
- (30) Watts, M; Anticancer Res 1997, V17, P71
- (31) Wong, M; Arteriosclerosis 1986, V6, P212 HCAPLUS
- (32) Zand, M; Cell Motil Cytoskeleton 1989, V13, P195 MEDLINE

L93 ANSWER 14 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2002:896034 HCAPLUS

DN 139:316714

ED Entered STN: 26 Nov 2002

TI The development of **combretastatin A4 phosphate** as a **vascular targeting** agent

AU Chaplin, David J.; Hill, Sally A.

CS Oxigene Inc., Watertown, MA, 02472, USA

SO International Journal of Radiation Oncology, Biology, Physics (2002), 54(5), 1491-1496

CODEN: IOBPD3; ISSN: 0360-3016

PB Elsevier Science Inc.

DT Journal

LA English

CC 1-6 (Pharmacology)

AB Purpose: This overview summarizes the preclin. development of tubulin-depolymg. agents as **vascular targeting** agents, leading to the identification of **combretastatin A4P** (**CA4P**). Methods and Materials: The murine tumor CaNT was implanted s.c. in the dorsum of CBA mice. **Vascular** function was determined after treatment using the perfusion marker Hoechst 33342 and fluorescence

microscopy. Tumor cell response was assessed by using an excision assay and by measuring the delay in growth of treated tumors. Results: At doses that approximated one-half the maximum tolerated dose (MTD) in CBA mice, none of the agents evaluated-i.e., taxol, melphalan, 5-fluorouracil, doxorubicin, cisplatin, gemcitabine, and irinotecan-induced any significant reduction in perfused **vascular** volume within the tumor mass. In contrast, **CA4P** at a dose of 100 mg/kg, which approximates one-fifth the MTD, induced a greater than 80% reduction in **vascular** function. Although colchicine did induce **vascular** shutdown, this occurred only at doses approximating the MTD. Histol. evaluation demonstrated that continued growth and repopulation of the tumor mass was the result of a surviving rim of viable tumor cells at the tumor periphery. Conclusion: These results confirm the ability of **CA4P** to selectively compromise **vascular** function in exptl. tumors, inducing extensive tumor cell death at well-tolerated doses. However, despite these effects, no growth retardation is obtained when **CA4P** is administered alone in a single dose. The continued growth and repopulation of the tumor mass occurs from a narrow rim of viable cells at the periphery. If, as is believed, these remaining cells are the ones most sensitive to conventional cytotoxic and macromol. approaches, **CA4P** and other **vascular targeting** agents offer considerable potential for enhancing the effectiveness of existing and emerging cancer therapies.

ST **combretastatin A4 phosphate vascular targeting agent cancer**

IT Carcinoma
(adenocarcinoma; **combretastatin A4 phosphate** as a tumor **vascular targeting agent**)

IT Drug interactions
(**combretastatin A4 phosphate** and other **vascular targeting agents** may enhance the effectiveness of other antitumor agents)

IT Antitumor agents
Blood vessel
(**combretastatin A4 phosphate** as a tumor **vascular targeting agent**)

IT Radiotherapy
(comparison treatment; **combretastatin A4 phosphate** as a tumor **vascular targeting agent**)

IT 222030-63-9, **Combretastatin A4 phosphate**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**combretastatin A4 phosphate** as a tumor **vascular targeting agent**)

IT 51-21-8, 5-Fluorouracil 148-82-3, Melphalan 15663-27-1, Cisplatin 23214-92-8, Doxorubicin 33069-62-4, Taxol 95058-81-4, Gemcitabine 97682-44-5, Irinotecan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(comparison compound; **combretastatin A4 phosphate** as a tumor **vascular targeting agent**)

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IT 222030-63-9, Combretastatin A4

phosphate

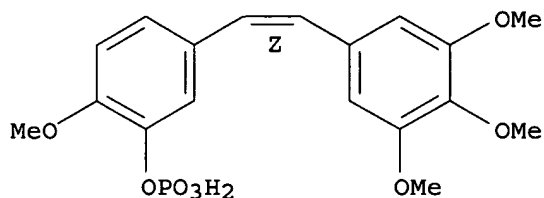
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(combretastatin A4 phosphate as a tumor vascular targeting agent)

RN 222030-63-9 HCAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen phosphate (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L93 ANSWER 15 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2002:794895 HCAPLUS

DN 138:297218

ED Entered STN: 20 Oct 2002

TI Schedule dependence of **combretastatin A4 phosphate** in transplanted and spontaneous tumor models

AU Hill, Sally A.; **Chaplin, David J.**; Lewis, Gemma; Tozer, Gillian M.

CS Tumour Microcirculation Group, Gray Cancer Institute, Mount Vernon Hospital, Northwood, HA6 2JR, UK

SO International Journal of Cancer (2002), 102(1), 70-74
CODEN: IJCNAW; ISSN: 0020-7136

PB Wiley-Liss, Inc.

DT Journal

LA English

CC 1-6 (Pharmacology)

AB Tubulin depolymg. drugs that selectively disrupt tumor-associated vasculature have recently been identified. The lead drug in this class, **combretastatin A4 phosphate (CA4P)**, has just completed Phase I clin. trial. Previous studies have focussed on the effects of single drug doses and have demonstrated little or no retardation of tumor growth when **CA4P** is used alone, but significant benefit when it is combined with conventional treatment. We have investigated the effects of multiple daily or twice daily dosing with **CA4P** on the vascular function, cell survival and growth of syngeneic and spontaneous breast cancers in mice. In both transplanted and spontaneous tumors significant growth retardation is observed if **CA4P** is administered daily (10 doses + 50 mg/kg), whereas no significant effects are seen if the same total dose (500 mg/kg) is administered as a single bolus injection. This effect is attributed, at least in part, to anti-proliferative effects on the tumor and endothelial cells, which retard the revascularization and repopulation of the tumor core that is initially necrosed by the drug treatment. Further investigation of dose scheduling showed that the initial anti-vascular effects of **CA4P** are enhanced by administering the drug in 2 equal doses separated between 2 and 6 h. The twice daily dosing schedule (25 mg/kg twice a day) produced increased growth retardation compared to the 50 mg/kg once a day schedule in the transplanted CaNT tumor. It did not do so in the spontaneous T138 tumor model. These studies indicate that the potential anti-tumor activity of **CA4P** when used as a single agent in clin. trials may be enhanced when used in multiple dose schedules.

ST **combretastatin A4 phosphate** antitumor breast cancer angiogenesis inhibitor

IT Angiogenesis inhibitors
Antitumor agents
Mammary gland, neoplasm
(schedule dependence of **combretastatin A4 phosphate** in transplanted and spontaneous tumor models)

IT 222030-63-9, **Combretastatin A4 phosphate**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(schedule dependence of **combretastatin A4 phosphate** in transplanted and spontaneous tumor models)

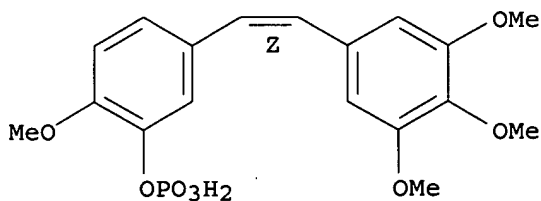
RE.CNT 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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- IT 222030-63-9, **Combretastatin A4 phosphate**
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (schedule dependence of **combretastatin A4 phosphate** in transplanted and spontaneous tumor models)
- RN 222030-63-9 HCAPLUS
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen phosphate (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L93 ANSWER 16 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:651667 HCAPLUS
DN 138:214971
ED Entered STN: 29 Aug 2002
TI Preclinical evaluation of the antitumor activity of the novel
vascular-targeting agent Oxi 4503
AU Hill, Sally A.; Tozer, Gillian M.; Pettit, George R.; Chaplin, David
J.
CS Gray Cancer Institute, Mount Vernon Hospital, Northwood, Middlesex, HA6
2JR, UK
SO Anticancer Research (2002), 22(3), 1453-1458
CODEN: ANTRD4; ISSN: 0250-7005
PB International Institute of Anticancer Research
DT Journal
LA English
CC 1-6 (Pharmacology)
AB Oxi 4503 is the **diphosphate** prodrug form of
combretastatin A1. At 1 mg/kg Oxi 4503 induced a >50%
reduction in functional vascular volume in mice, which increased to ≥80%
following doses of 10, 25 and 50 mg/kg. In contrast,
combretastatin A4 phosphate (CA4P)
induced approx. 40% vascular shutdown at 50 mg/kg but had no measurable
effect at 10 mg/kg. In addition to these vascular effects, Oxi 4503 at 100,
200 and 400 mg/kg retarded the growth of established murine adenocarcinoma
CaNT tumors in mice. No significant growth retardation was obtained with
single doses of ≤400 mg **CA4P**/kg. These studies have
identified Oxi 4503 as a preclin. development candidate with more potent
antivascular and antitumor effects than **CA4P** when used as a
single agent.
ST Oxi 4503 **combretastatin** prodrug antiangiogenesis inhibitor
antitumor adenocarcinoma
IT Carcinoma
(adenocarcinoma; antitumor and antiangiogenic effects of Oxi 4503, a
prodrug of **combretastatin A1**, vs.
combretastatin A4 phosphate)
IT Angiogenesis inhibitors
(antitumor and antiangiogenic effects of Oxi 4503, a prodrug of
combretastatin A1, vs. **combretastatin**
A4 phosphate)
IT Antitumor agents
Neoplasm
(preclin. evaluation of the antitumor activity of the novel
vascular-targeting agent Oxi 4503)
IT Drug delivery systems
(prodrugs; antitumor and antiangiogenic effects of Oxi 4503, a prodrug
of **combretastatin A1**, vs. **combretastatin**
A4 phosphate)
IT 222030-63-9, **Combretastatin A4**
phosphate 288847-35-8
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(antitumor and antiangiogenic effects of Oxi 4503, a prodrug of
combretastatin A1, vs. **combretastatin**
A4 phosphate)
RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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IT 222030-63-9, **Combretastatin A4**

phosphate 288847-35-8

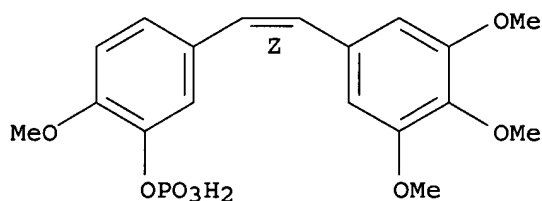
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(antitumor and antiangiogenic effects of Oxi 4503, a prodrug of **combretastatin A1**, vs. **combretastatin A4 phosphate**)

RN 222030-63-9 HCAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen phosphate (9CI) (CA INDEX NAME)

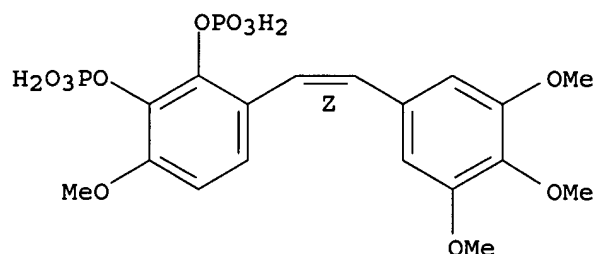
Double bond geometry as shown.



RN 288847-35-8 HCAPLUS

CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, bis(dihydrogen phosphate) (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L93 ANSWER 17 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
 AN 2002:555278 HCAPLUS
 DN 137:119643
 ED Entered STN: 26 Jul 2002
 TI Methods using a **combretastatin** compound combined with an
 antitumor agent for modulating tumor growth and metastasis
 IN Lee, Francis Y.; Peck, Ronald; **Chaplin, David**; Pero, Ronald;
 Edvardsen, Klaus
 PA Bristol-Myers Squibb Company, USA; **Oxigene, Inc.**
 SO PCT Int. Appl., 69 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 IC ICM A01N057-00
 ICS A61K038-00
 CC 1-6 (Pharmacology)
 Section cross-reference(s): 63

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002056692	A1	20020725	WO 2001-US50261	20011220 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
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CA 2432792	AA	20020725	CA 2001-2432792	20011220 <--
EP 1351573	A1	20031015	EP 2001-994435	20011220 <--
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JP 2004523517	T2	20040805	JP 2002-557211	20011220 <--
PRAI US 2000-258195P	P	20001222		<--
WO 2001-US50261	W	20011220		<--

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2002056692	ICM	A01N057-00
	ICS	A61K038-00
WO 2002056692	ECLA	A61K045/06
JP 2004523517	FTERM	4C084/AA02; 4C084/AA03; 4C084/AA19; 4C084/BA44; 4C084/MA02; 4C084/MA13; 4C084/MA17; 4C084/MA22; 4C084/MA23; 4C084/MA43; 4C084/MA52; 4C084/MA56;

4C084/MA59; 4C084/MA66; 4C084/NA05; 4C084/NA06;
 4C084/ZA362; 4C084/ZB262; 4C084/ZC412; 4C086/AA01;
 4C086/AA02; 4C086/BA02; 4C086/CB22; 4C086/DA34;
 4C086/HA12; 4C086/HA28; 4C086/MA02; 4C086/MA04;
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 4C086/MA66; 4C086/NA05; 4C086/NA06; 4C086/ZA36;
 4C086/ZB26; 4C086/ZC41; 4C088/AB12; 4C088/AC06;
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 4C206/MA79; 4C206/MA86; 4C206/NA05; 4C206/NA06;
 4C206/ZA36; 4C206/ZB26; 4C206/ZC41

<--

AB Methods and pharmaceutical compns. for modulating tumor growth or metastasis are provided. The methods of the invention use combinations of a **combretastatin** compound and an antitumor agent.

ST **combretastatin** compd antitumor agent combination neoplasm metastasis treatment

IT Pseudomonas
 (BR96-sFv-PE40 immunoconjugate; **combretastatin** compound combined with antitumor agent for modulating tumor growth and metastasis)

IT Antitumor agents
 (antibiotic; **combretastatin** compound combined with antitumor agent for modulating tumor growth and metastasis)

IT Nutrients
 (antinutrients; **combretastatin** compound combined with antitumor agent for modulating tumor growth and metastasis)

IT Antibiotics
 (antitumor; **combretastatin** compound combined with antitumor agent for modulating tumor growth and metastasis)

IT Mammary gland, neoplasm
 Ovary, neoplasm
 (carcinoma; **combretastatin** compound combined with antitumor agent for modulating tumor growth and metastasis)

IT Intestine, neoplasm
 (colon; **combretastatin** compound combined with antitumor agent for modulating tumor growth and metastasis)

IT Alkylating agents, biological
 Antitumor agents
 Circulation
 Drug delivery systems
 Drug interactions
 Human
 Immunotherapy
 Mammary gland, neoplasm
 Neoplasm
 Pharmacokinetics
 Radiotherapy
 (**combretastatin** compound combined with antitumor agent for modulating tumor growth and metastasis)

IT Antiestrogens
 Taxanes
 RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

- (**combretastatin** compound combined with antitumor agent for modulating tumor growth and metastasis)
- IT Toxins
 RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (exotoxins, BR96-sFv-PE40 immunoconjugate; **combretastatin** compound combined with antitumor agent for modulating tumor growth and metastasis)
- IT Sarcoma
 (fibrosarcoma; **combretastatin** compound combined with antitumor agent for modulating tumor growth and metastasis)
- IT Drug delivery systems
 (immunotoxins; **combretastatin** compound combined with antitumor agent for modulating tumor growth and metastasis)
- IT Carcinoma
 (mammary; **combretastatin** compound combined with antitumor agent for modulating tumor growth and metastasis)
- IT Neoplasm
 (metastasis; **combretastatin** compound combined with antitumor agent for modulating tumor growth and metastasis)
- IT Mitosis
 (mitotic inhibitors; **combretastatin** compound combined with antitumor agent for modulating tumor growth and metastasis)
- IT Antibodies and Immunoglobulins
 RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (monoclonal, conjugates, BR96-sFv-PE40 immunoconjugate; **combretastatin** compound combined with antitumor agent for modulating tumor growth and metastasis)
- IT Carcinoma
 (ovarian; **combretastatin** compound combined with antitumor agent for modulating tumor growth and metastasis)
- IT Drug delivery systems
 (prodrugs; **combretastatin** compound combined with antitumor agent for modulating tumor growth and metastasis)
- IT Drug interactions
 (synergistic; **combretastatin** compound combined with antitumor agent for modulating tumor growth and metastasis)
- IT 50-07-7, Mitomycin C 50-18-0, Cytosine 50-76-0, Dactinomycin 51-21-8, 5-Fluorouracil 51-75-2, Mechlorethamine 57-22-7, Vincristin 58-05-9, Leucovorin 59-05-2, Methotrexate 147-94-4, Cytarabine 148-82-3, Melphalan 154-93-8, Carmustine 305-03-3, Chlorambucil 595-33-5, Megace 865-21-4, Vinblastine 3778-73-2, Ifosfamide 4342-03-4, Dacarbazine 11056-06-7, Bleomycin 13010-20-3D, Nitrosourea, derivs. 13010-47-4, Lomustine 15663-27-1, Cisplatin 20830-81-3, Daunorubicin 21679-14-1, Fludarabine 23214-92-8, Doxorubicin 25316-40-9, Adriamycin 33069-62-4, Paclitaxel 33419-42-0, Etoposide 41575-94-4, Carboplatin 58957-92-9, Idarubicin 61825-94-3, Oxaliplatin 71486-22-1, Vinorelbine 74381-53-6, Lupron 74578-38-4, UFT 95058-81-4, Gemcitabine 100286-90-6, CPT-11 107868-30-4, Exemestane 114977-28-5, Docetaxel 117091-64-2, Etoposide phosphate 120511-73-1, Anastrozole 121584-18-7, Valspodar 123948-87-8, Topotecan 146426-40-6, Flavopiridol 180288-69-1, Herceptin 184475-35-2, Iressa 252916-29-3, SU6668 443913-73-3
 RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (**combretastatin** compound combined with antitumor agent for modulating tumor growth and metastasis)
- IT 109971-63-3, **Combretastatin A1**
 109971-63-3D, **Combretastatin A1**, derivs.

117048-59-6, Combretastatin A4

117048-59-6D, Combretastatin A4, derivs.

168555-66-6 288847-34-7

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(combretastatin compound combined with antitumor agent for modulating tumor growth and metastasis)

IT 143180-75-0

RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibitors; combretastatin compound combined with antitumor agent for modulating tumor growth and metastasis)

IT 9039-48-9, Aromatase

RL: BSU (Biological study, unclassified); BIOL (Biological study) (nonsteroidal inhibitors; combretastatin compound combined with antitumor agent for modulating tumor growth and metastasis)

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Oxigene Inc; WO 0048606 A1 2000 HCAPLUS

(2) Pettit; US 4996237 A 1991 HCAPLUS

(3) Pettit; US 5561122 A 1996 HCAPLUS

IT 109971-63-3, Combretastatin A1

109971-63-3D, Combretastatin A1, derivs.

117048-59-6, Combretastatin A4

117048-59-6D, Combretastatin A4, derivs.

168555-66-6 288847-34-7

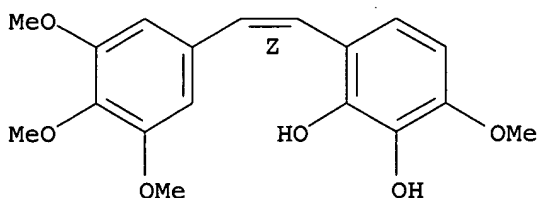
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(combretastatin compound combined with antitumor agent for modulating tumor growth and metastasis)

RN 109971-63-3 HCAPLUS

CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-(9CI) (CA INDEX NAME)

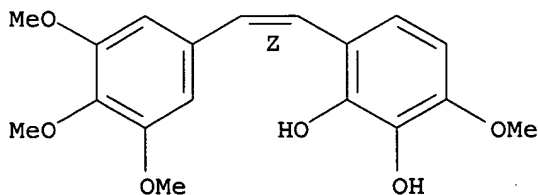
Double bond geometry as shown.



RN 109971-63-3 HCAPLUS

CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-(9CI) (CA INDEX NAME)

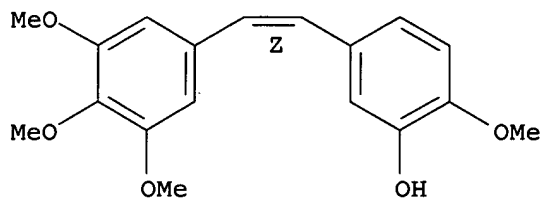
Double bond geometry as shown.



RN 117048-59-6 HCAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

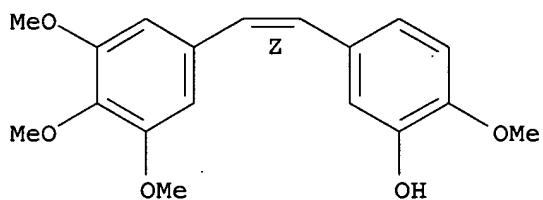
Double bond geometry as shown.



RN 117048-59-6 HCAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

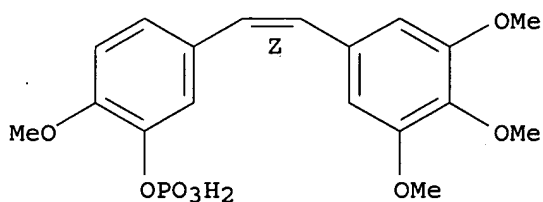
Double bond geometry as shown.



RN 168555-66-6 HCAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen phosphate, disodium salt (9CI) (CA INDEX NAME)

Double bond geometry as shown.

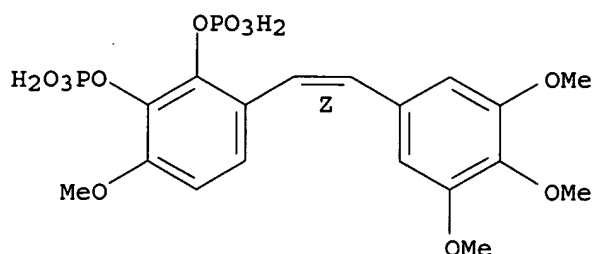


● 2 Na

RN 288847-34-7 HCAPLUS

CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, bis(dihydrogen phosphate), tetrasodium salt (9CI) (CA INDEX NAME)

Double bond geometry as shown.



● 4 Na

L93 ANSWER 18 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2002:72094 HCAPLUS

DN 136:134622

ED Entered STN: 25 Jan 2002

TI Methods of synthesizing prodrugs of **combretastatin A-4**

IN Seyedi, Faye; Gale, Jonathan; Haider, Reem; Hoare, John

PA **Oxigene, Inc., USA**

SO PCT Int. Appl., 41 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C07D417-12

ICS C07D211-58; A61K031-445; A61K031-41; C07D417-12; C07D285-00;
C07D211-00

CC 26-9 (Biomolecules and Their Synthetic Analogs)

FAN.CNT 1

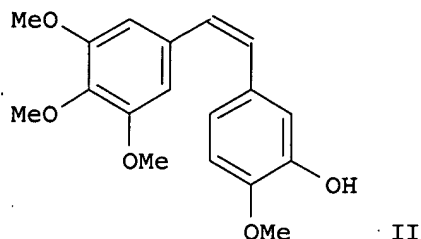
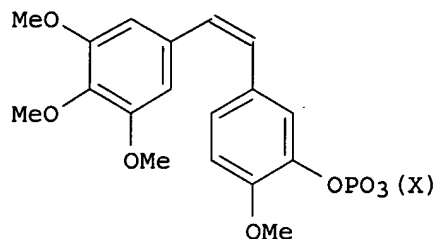
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PI	WO 2002006279	A1	20020124	WO 2001-US22403	20010717 <--
	WO 2002006279	C1	20020418		
	WO 2002006279	C2	20030403		
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	CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,				
	GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,				
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	RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ,				
	VN, YU, ZA, ZW				
	RW:				
	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG,				
	KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR,				
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	US 2002119951	A1	20020829	US 2001-908321	20010717 <--
	US 6743937	B2	20040601		
PRAI	US 2000-218766P	P	20000717	<--	

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2002006279	ICM	C07D417-12
	ICS	C07D211-58; A61K031-445; A61K031-41; C07D417-12; C07D285-00; C07D211-00
WO 2002006279	ECLA	C07F009/12+J
US 2002119951	NCL	558/210.000

ECLA C07F009/12+J

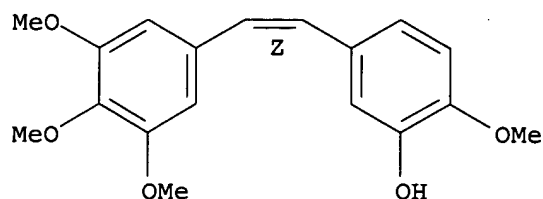
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OS CASREACT 136:134622
GI

- AB The present invention discloses improved methods of synthesizing a **phosphate ester of combretastatin A-4**, such as I [X = HZ1, Z2; Z1 = Na⁺, Li⁺; Z2 = Mg²⁺, Zn²⁺, Ca²⁺, Cs²⁺, imidazole, morpholine, etc.], and trans-isomers thereof. Thus, **combretastatin A-4 (II)** is reacted with dibenzylphosphite in the presence of carbon tetrabromide, or with 2,2,2-trichloroethyl phosphorodichloridate, to form a **phosphate ester of combretastatin A-4** with protecting groups thereon.
- ST **combretastatin A4 phosphate prodrug prepn**
phosphorylation
- IT Protective groups
(hydroxyl; in synthesizing prodrugs of **combretastatin A-4**)
- IT Pulverization
Recrystallization
(methods of synthesizing prodrugs of **combretastatin A-4**)
- IT Phosphorylation
(of **combretastatin A-4** in synthesizing prodrugs of **combretastatin A-4**)
- IT Drug delivery systems
(prodrugs; methods of synthesizing prodrugs of **combretastatin A-4**)
- IT 2857-97-8, Bromotrimethylsilane 12714-27-1, Zinc amalgam 39314-60-8, Copper amalgam
RL: RGT (Reagent); RACT (Reactant or reagent)
(deprotecting agent in synthesizing prodrugs of **combretastatin A-4**)
- IT 121-44-8, Triethylamine, miscellaneous 558-13-4, Carbon tetrabromide
RL: MSC (Miscellaneous)
(for phosphorylation in synthesizing prodrugs of **combretastatin A-4**)
- IT 17672-53-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(for phosphorylation in synthesizing prodrugs of **combretastatin A-4**)
- IT 60-29-7, Ether, miscellaneous 67-64-1, Acetone, miscellaneous 75-05-8, Acetonitrile, miscellaneous 108-88-3, Toluene, miscellaneous 109-99-9, Tetrahydrofuran, miscellaneous 141-78-6, Ethyl acetate, miscellaneous 142-82-5, Heptane, miscellaneous 7732-18-5, Water, miscellaneous
RL: MSC (Miscellaneous)
(methods of synthesizing prodrugs of **combretastatin A**)

- 4)
- IT 117048-59-6P, **Combretastatin A-4**
 RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
 (methods of synthesizing prodrugs of **combretastatin A**)
- 4)
- IT 168555-66-6P 222030-63-9P 226989-84-0P
 229178-29-4P 229178-30-7P 229178-31-8P
 229178-32-9P 229178-34-1P 229178-35-2P 229178-36-3P 229178-37-4P
 229178-38-5P 229178-39-6P 229178-40-9P 229178-41-0P 229178-42-1P
 229178-43-2P 229178-45-4P 229178-46-5P 229178-47-6P 229178-48-7P
 391671-17-3P 391671-18-4P 391671-20-8P
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (methods of synthesizing prodrugs of **combretastatin A**)
- 4)
- IT 67-56-1, Methanol, reactions 76-83-5, Trityl chloride 109-72-8, n-Butyl lithium, reactions 124-41-4, Sodium methoxide 603-35-0, Triphenylphosphine, reactions 621-59-0, Isovanillin 3840-31-1, 3,4,5-Trimethoxybenzyl alcohol 7647-01-0, Hydrochloric acid, reactions 7789-60-8, Phosphorus tribromide 17176-77-1, Dibenzylphosphite
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (methods of synthesizing prodrugs of **combretastatin A**)
- 4)
- IT 61240-20-8P 208465-88-7P 391671-21-9P 391671-22-0P 391671-23-1P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (methods of synthesizing prodrugs of **combretastatin A**)
- 4)
- IT 762-04-9, Diethylphosphite 868-85-9, Dimethylphosphite 1809-19-4, Dibutylphosphite 1809-20-7, Di-isopropylphosphite 1809-21-8, Dipropylphosphite 4712-55-4, Diphenylphosphite 13086-84-5, Di-tert-butylphosphite
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (phosphorylating agent in synthesizing prodrugs of **combretastatin A-4**)
- IT 144-55-8, Sodium bicarbonate, reactions 16029-98-4, Iodotrimethylsilane
 RL: RGT (Reagent); RACT (Reactant or reagent)
 (phosphorylating agent in synthesizing prodrugs of **combretastatin A-4**)
- IT 117048-59-6P, **Combretastatin A-4**
 RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
 (methods of synthesizing prodrugs of **combretastatin A**)
- 4)
- RN 117048-59-6 HCAPLUS
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



IT 168555-66-6P 222030-63-9P 226989-84-0P
 229178-29-4P 229178-30-7P 229178-31-8P
 391671-17-3P 391671-18-4P 391671-20-8P

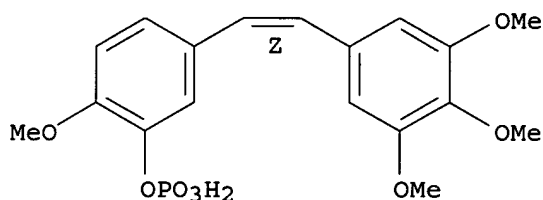
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
 (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
 (Uses)

(methods of synthesizing prodrugs of **combretastatin A**
 -4)

RN 168555-66-6 HCAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen
 phosphate, disodium salt (9CI) (CA INDEX NAME)

Double bond geometry as shown.

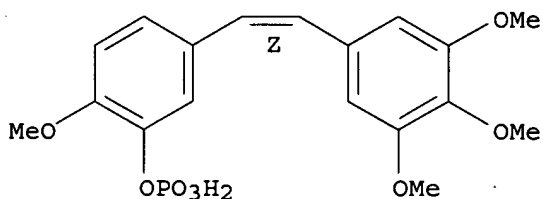


● 2 Na

RN 222030-63-9 HCAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen
 phosphate (9CI) (CA INDEX NAME)

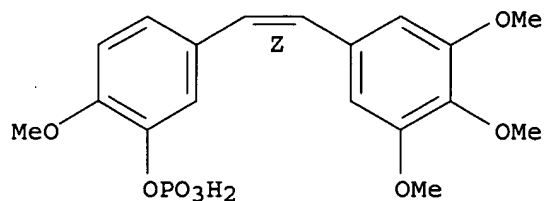
Double bond geometry as shown.



RN 226989-84-0 HCAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen
 phosphate, monosodium salt (9CI) (CA INDEX NAME)

Double bond geometry as shown.

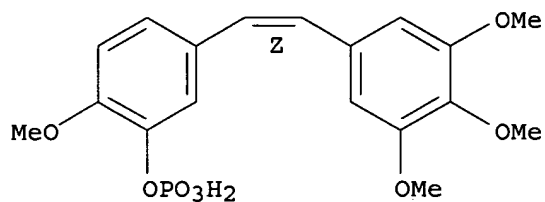


● Na

RN 229178-29-4 HCAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen phosphate, calcium salt (1:1) (9CI) (CA INDEX NAME)

Double bond geometry as shown.

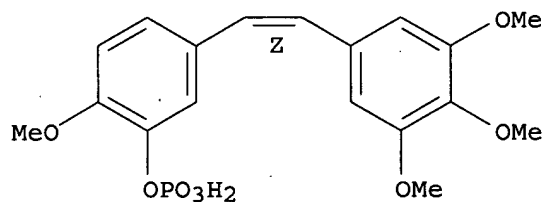


● Ca

RN 229178-30-7 HCAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen phosphate, monocationic salt (9CI) (CA INDEX NAME)

Double bond geometry as shown.

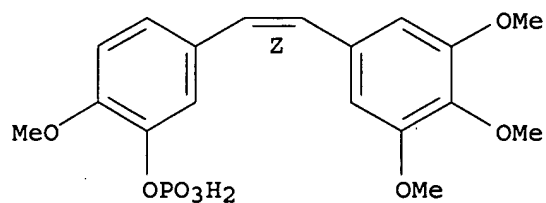


● Cs

RN 229178-31-8 HCAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen phosphate, monolithium salt (9CI) (CA INDEX NAME)

Double bond geometry as shown.



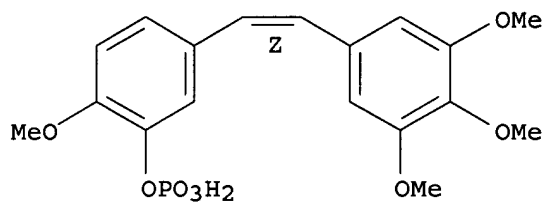
● Li

RN 391671-17-3 HCAPLUS
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen phosphate, manganese salt (9CI) (CA INDEX NAME)

CM 1

CRN 222030-63-9
 CMF C18 H21 O8 P

Double bond geometry as shown.



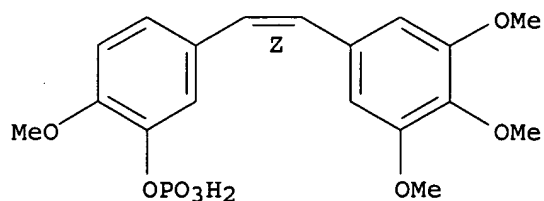
CM 2

CRN 7439-96-5
 CMF Mn

Mn

RN 391671-18-4 HCAPLUS
 CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen phosphate, monopotassium salt (9CI) (CA INDEX NAME)

Double bond geometry as shown.

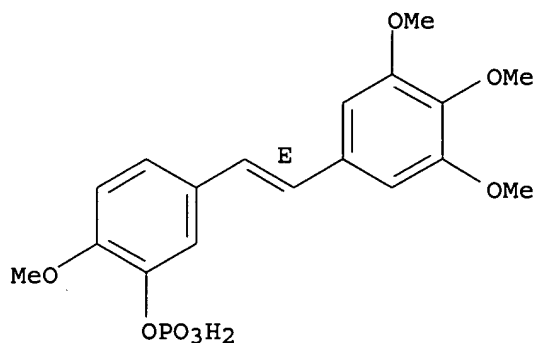


● K

RN 391671-20-8 HCAPLUS

CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen phosphate (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L93 ANSWER 19 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2001:659027 HCAPLUS

DN 136:295

ED Entered STN: 09 Sep 2001

TI Mechanisms associated with tumor vascular shut-down induced by **combretastatin A-4 phosphate**:

intravital microscopy and measurement of vascular permeability

AU Tozer, Gillian M.; Prise, Vivien E.; Wilson, John; Cemazar, Maja; Shan, Siqing; Dewhurst, Mark W.; Barber, Paul R.; Vojnovic, Borivoj; **Chaplin, David J.**

CS Gray Cancer Institute, Mount Vernon Hospital, Northwood, HA6 2JR, UK

SO Cancer Research (2001), 61(17), 6413-6422

CODEN: CNREA8; ISSN: 0008-5472

PB American Association for Cancer Research

DT Journal

LA English

CC 1-6 (Pharmacology)

AB The tumor **vascular** effects of the tubulin destabilizing agent disodium **combretastatin A-4 3-O-**

phosphate (CA-4-P) were investigated in the rat P22 tumor growing in a dorsal skin flap window chamber implanted into BD9 rats. CA-4-P is in clin. trial as a tumor **vascular targeting** agent.

In animal tumors, it can cause the shut-down of blood flow, leading to extensive tumor cell necrosis. However, the mechanisms leading to **vascular** shut-down are still unknown. Tumor **vascular**

effects were visualized and monitored online before and after the administration of two doses of CA-4-P (30 and 100 mg/kg) using intravital microscopy. The combined effect of CA-4-P and systemic nitric oxide synthase (NOS) inhibition using N^ω-nitro-L-arginine (L-NNA) was also assessed, because this combination has been shown previously to have a potentiating effect. The early effect of CA-4-P on tumor **vascular** permeability to albumin was determined to assess whether this could be involved in the mechanism of action of the drug. Tumor blood flow reduction was extremely rapid after CA-4-P treatment, with red cell velocity decreasing throughout the observation period and dropping to <5% of the starting value by 1 h. NOS inhibition alone caused a 50% decrease in red cell velocity, and the combined treatment of CA-4-P and NOS inhibition was approx. additive. The mechanism of blood flow reduction was very different for NOS inhibition and CA-4-P. That of NOS inhibition could be explained by a decrease in vessel diameter, which was most profound on the arteriolar side of the tumor circulation. In contrast, the effects of CA-4-P resembled an acute inflammatory reaction resulting in a visible loss of a large proportion of the smallest blood vessels. There was some return of visible vasculature at 1 h after treatment, but the blood in these vessels was static or nearly so, and many of the vessels were distended. The hematocrit within larger draining tumor venules tended to increase at early times after CA-4-P, suggesting fluid loss from the blood. The stacking of red cells to form rouleaux was also a common feature, coincident with slowing of blood flow; and these two factors would lead to an increase in viscous resistance to blood flow. Tumor **vascular** permeability to albumin was increased to .apprx.160% of control values at 1 and 10 min after treatment. This could lead to an early decrease in tumor blood flow via an imbalance between intravascular and tissue pressures and/or an increase in blood viscosity as a result of increased hematocrit. These results suggest a mechanism of action of CA-4-P in vivo. Combination of CA-4-P with a NOS inhibitor has an additive effect, which it may be possible to exploit therapeutically.

- ST vessel shut **combretastatin A4 phosphate**
- IT intravital permeability
- IT Drug interactions
 - (additive; mechanisms associated with tumor vascular shut-down induced by **combretastatin A-4 phosphate**)
- IT Circulation
- IT Hematocrit
 - (mechanisms associated with tumor vascular shut-down induced by **combretastatin A-4 phosphate**)
- IT Blood vessel
 - (permeability; mechanisms associated with tumor vascular shut-down induced by **combretastatin A-4 phosphate**)
- IT Biological transport
 - (permeation, vascular; mechanisms associated with tumor vascular shut-down induced by **combretastatin A-4 phosphate**)
- IT 125978-95-2, NO synthase
 - RL: BSU (Biological study, unclassified); BIOL (Biological study)
 - (mechanisms associated with tumor vascular shut-down induced by **combretastatin A-4 phosphate**)
- IT 168555-66-6
 - RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 - (mechanisms associated with tumor vascular shut-down induced by **combretastatin A-4 phosphate**)
- IT 2149-70-4, Nitro-arginine
 - RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)

(mechanisms associated with tumor vascular shut-down induced by
combretastatin A-4 phosphate)

RE.CNT 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD
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- (33) Pettit, G; Experientia 1989, V45, P205
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- (35) Seed, L; Surgery 1940, V7, P696
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- (37) Tozer, G; Br J Cancer 1993, V67, P981 HCAPLUS
- (38) Tozer, G; Br J Cancer 1994, V70, P1040 MEDLINE
- (39) Tozer, G; Cancer Res 1997, V57, P948 HCAPLUS
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IT 168555-66-6

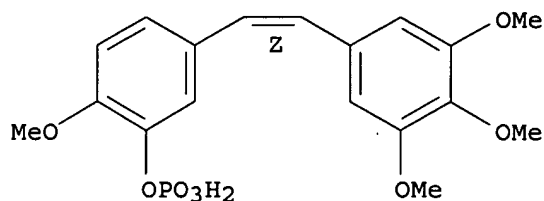
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU
(Therapeutic use); BIOL (Biological study); USES (Uses)

(mechanisms associated with tumor vascular shut-down induced by
combretastatin A-4 phosphate)

RN 168555-66-6 HCAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen
phosphate, disodium salt (9CI) (CA INDEX NAME)

Double bond geometry as shown.



●2 Na

L93 ANSWER 20 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
 AN 2001:465870 HCAPLUS
 DN 135:238667
 ED Entered STN: 28 Jun 2001
 TI Eradication of colorectal xenografts by combined radioimmunotherapy and **combretastatin A-4 3-O-phosphate**
 AU Pedley, R. Barbara; Hill, Sally A.; Boxer, Geoffrey M.; Flynn, Aiden A.; Boden, Robert; Watson, Rebecca; Dearling, Jason; **Chaplin, David J.**; Begent, Richard H. J.
 CS Department of Oncology, Royal Free and University College Medical School, London, NW3 2PF, UK
 SO Cancer Research (2001), 61(12), 4716-4722
 CODEN: CNREA8; ISSN: 0008-5472
 PB American Association for Cancer Research
 DT Journal
 LA English
 CC 8-9 (Radiation Biochemistry)
 AB Solid tumors have a heterogeneous pathophysiol., which has a major impact on therapy. Using SW1222 colorectal xenografts grown in nude mice, we have shown that antibody-targeted radioimmunotherapy (RIT) effectively treated the well-perfused tumor rim, producing regressions for .apprx.35 days, but was less effective at the more hypoxic center. By 72 h after RIT, the number of apoptotic cells rose from an overall value of 1% in untreated tumors to 35% at the tumor periphery and 10% at the center. The antivascular agent disodium **combretastatin A-4 3-O-phosphate** (CA4-P) rapidly reduced tumor blood flow to 62% of control values by 1 h, 23% by 3 h, and between 32-36% from 6 to 24 h after administration. This created central hemorrhagic necrosis, but a peripheral rim of cells continued to grow, and survival was unaffected. Changes in the pattern of perfusion across the tumor over time were zonal. Untreated mice showed perfusion throughout the tumor, with greatest activity at the rim. There was an overall reduction at 1 h, and total cessation of central perfusion from 3 h onward. A narrow peripheral rim of perfusion was always present, which increased in intensity and extent between 6 and 24 h, either through reperfusion or new vessel growth. Combining these two complementary therapies (7.4 MBq ¹³¹I-labeled anti-carcinoembryonic antigen IgG i.v. plus a single 200 mg/kg dose of CA4-P i.p.) produced complete cures in five of six mice for >9 mo. Allowing maximal tumor localization of antibody (48 h) before blood flow inhibition by CA4-P increased tumor retention by two to three times control levels by 96 h without altering normal tissue levels, as confirmed by gamma counting and phosphor image anal. The success of this combined, synergistic therapy was probably the result of several factors: (a) the killing of tumor cells in the outer, radiosensitive region by targeted radiotherapy; (b) enhancement of RIT by entrapment of addnl. radioantibody

after **combretastatin**-induced vessel collapse; and (c) destruction of the central, more hypoxic and radioresistant region by CA4-P. This work demonstrates the need to consider cancer treatment in a biol. heterogeneous setting, if results are to be effectively translated to the clinic.

- ST colorectal cancer iodine 131 IgG radioimmunotherapy **combretastatin**
 IT Immunoglobulins
 RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
 (G, radiolabeled; colorectal cancer treatment by radioimmunotherapy and **combretastatin A-4 3-O-phosphate**)
- IT Immunoradiotherapy
 (colorectal cancer treatment by radioimmunotherapy and **combretastatin A-4 3-O-phosphate**)
- IT Intestine, neoplasm
 (colorectal; colorectal cancer treatment by radioimmunotherapy and **combretastatin A-4 3-O-phosphate**)
- IT Antibodies
 RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
 (monoclonal, iodo, labeled with iodine-131; colorectal cancer treatment by radioimmunotherapy and **combretastatin A-4 3-O-phosphate**)
- IT Drug interactions
 (synergistic; colorectal cancer treatment by radioimmunotherapy and **combretastatin A-4 3-O-phosphate**)
- IT Carcinoembryonic antigen
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (131I-labeled IgGs against; colorectal cancer treatment by radioimmunotherapy and **combretastatin A-4 3-O-phosphate**)
- IT 168555-66-6
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (colorectal cancer treatment by radioimmunotherapy and **combretastatin A-4 3-O-phosphate**)
- IT 10043-66-0D, iodine 131, IgG labeled with, biological studies
 RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
 (colorectal cancer treatment by radioimmunotherapy and **combretastatin A-4 3-O-phosphate**)

RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
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IT 168555-66-6

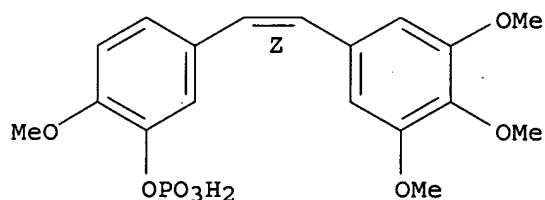
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(colorectal cancer treatment by radioimmunotherapy and
combretastatin A-4 3-O-phosphate)

RN 168555-66-6 HCAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen phosphate, disodium salt (9CI) (CA INDEX NAME)

Double bond geometry as shown.



●2 Na

L93 ANSWER 21 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
 AN 2001:294493 HCAPLUS
 DN 135:220760
 ED Entered STN: 26 Apr 2001
 TI Effects of **combretastatin A4 phosphate** on
 endothelial cell morphology in vitro and relationship to tumor
vascular targeting activity in vivo
 AU Galbraith, Susan M.; **Chaplin, David J.**; Lee, Francesca;
 Stratford, Michael R. L.; Locke, Rosalind J.; Vojnovic, Borivoj; Tozer,
 Gillian M.
 CS Tumour Microcirculation Group, Gray Laboratory Cancer Research Trust,
 Northwood, HA6 2JR, UK
 SO Anticancer Research (2001), 21(1A), 93-102
 CODEN: ANTRD4; ISSN: 0250-7005
 PB International Institute of Anticancer Research
 DT Journal
 LA English

CC 1-6 (Pharmacology)

AB **Combretastatin A4 Phosphate (CA4P)**

is a tubulin binding agent which causes rapid tumor vascular shutdown. It has anti-proliferative and apoptotic effects on dividing endothelial cells after prolonged exposure, but these effects occur on a much longer time scale than the reduction in tumor blood flow. This study compared the time course of **CA4P** effects on endothelial cell shape and reduction in red cell velocity. Endothelial cell area and form factor ($1 - 4\pi + \text{area} + \text{perimeter} - 2$) were measured for proliferating and confluent HUVECs after **CA4P** treatment. Recovery of shape after **CA4P** and colchicine was compared. Window chamber studies of tumors were used to measure red cell velocity. 70% Reduction in red cell velocity and 44% reduction in HUVEC form factor occurred by 10 min. Proliferating HUVECs underwent greater cell shape change after **CA4P**, which occurred at lower doses than for confluent cells. Cell shape recovered 24 h after 30 min exposure to **CA4P**, but not after colchicine. The similar time course of cell shape change and red cell velocity reduction suggests endothelial cell shape change may be involved early in the in vivo events leading to vascular shutdown. Differences in the recovery from the shape changes induced by **CA4P** and colchicine could underlie the different toxicity profiles of these drugs.

ST **combretastatin A4** endothelial cell morphol antitumor

IT Antitumor agents

Apoptosis

Cell morphology

(effects of **combretastatin A4 phosphate** on endothelial cell morphol. in vitro and relationship to tumor **vascular targeting** activity in vivo)

IT Blood vessel

(endothelium; effects of **combretastatin A4 phosphate** on endothelial cell morphol. in vitro and relationship to tumor **vascular targeting** activity in vivo)

IT 64-86-8, Colchicine

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(effects of **combretastatin A4 phosphate** on endothelial cell morphol. in vitro and relationship to tumor **vascular targeting** activity in vivo)

IT 117048-59-6, **combretastatin A4**
168555-66-6, **combretastatin A4 disodium phosphate**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(effects of **combretastatin A4 phosphate** on endothelial cell morphol. in vitro and relationship to tumor **vascular targeting** activity in vivo)

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IT 117048-59-6, **combretastatin A4**

168555-66-6, **combretastatin A4** disodium

phosphate

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(effects of **combretastatin A4 phosphate**

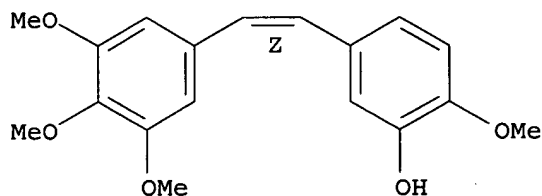
on endothelial cell morphol. in vitro and relationship to tumor

vascular targeting activity in vivo)

RN 117048-59-6 HCAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

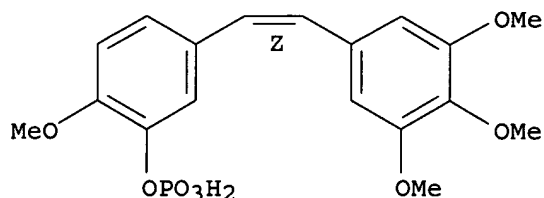
Double bond geometry as shown.



RN 168555-66-6 HCAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen phosphate, disodium salt (9CI) (CA INDEX NAME)

Double bond geometry as shown.



●2 Na

L93 ANSWER 22 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2000:717223 HCAPLUS

DN 134:216909

ED Entered STN: 11 Oct 2000

TI Determinants of anti-vascular action by **combretastatin A-4 phosphate**: role of nitric oxide

AU Parkins, C. S.; Holder, A. L.; Hill, S. A.; Chaplin, D. J.; Tozer, G. M.

CS Tumour Microcirculation Group, Gray Laboratory Cancer Research Trust, Mount Vernon Hospital, Northwood, HA6 2JR, UK

SO British Journal of Cancer (2000), 83(6), 811-816
CODEN: BJCAAI; ISSN: 0007-0920

PB Harcourt Publishers Ltd.

DT Journal

LA English

CC 1-6 (Pharmacology)

AB The anti-vascular action of the tubulin binding agent.

combretastatin A-4 phosphate

(CA-4-P) has been quantified in two types of murine tumor, the breast adenocarcinoma CaNT and the round cell sarcoma SaS. The functional vascular volume, assessed using a fluorescent carbocyanine dye, was significantly reduced at 18 h after CA-4-P treatment in both tumor types, although the degree of reduction was very different in the two tumors. The SaS tumor, which has a higher nitric oxide synthase (NOS) activity than the CaNT tumor, showed approx.10-fold greater resistance to vascular damage by CA-4-P. This is consistent with our previous findings, which showed that NO exerts a protective action against this drug. Simultaneous administration of CA-4-P with a NOS inhibitor, N^ω-nitro-L-arginine (L-NNA), resulted in enhanced vascular damage and cytotoxicity in both tumor types. Administration of diethylamine NO, an NO donor, conferred protection against the vascular damaging effects. Following treatment with CA-4-P, neutrophil infiltration into the tumors, measured by myeloperoxidase (MPO) activity, was significantly increased. Levels of MPO activity also correlated with the levels of vascular injury and cytotoxicity measured in both tumor types. Neutrophilic MPO generates free radicals and may therefore contribute to the vascular damage associated with CA-4-P treatment. MPO activity was significantly increased in the presence of L-NNA, suggesting that the protective effect of NO against CA-4-P-induced vascular injury may be, at least partially, mediated by limiting neutrophil infiltration. The data are consistent with the hypothesis that neutrophil action contributes to vascular injury by CA-4-P and that NO generation acts to protect the tumor vasculature against CA4-P-induced injury. The protective effect of NO is probably associated

with an anti-neutrophil action.

ST antitumor **combretastatin A4 phosphate**
angiogenesis inhibitor nitric oxide

IT Drug resistance
(antitumor; determinants of anti-vascular action by
combretastatin A-4 phosphate:
role of nitric oxide)

IT Angiogenesis inhibitors
(determinants of anti-vascular action by **combretastatin**
A-4 phosphate: role of nitric oxide)

IT Neutrophil
(infiltration; determinants of anti-vascular action by
combretastatin A-4 phosphate:
role of nitric oxide)

IT Antitumor agents
(resistance to; determinants of anti-vascular action by
combretastatin A-4 phosphate:
role of nitric oxide)

IT 168555-66-6
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(determinants of anti-vascular action by **combretastatin**
A-4 phosphate: role of nitric oxide)

IT 125978-95-2, Nitric oxide synthase
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(determinants of anti-vascular action by **combretastatin**
A-4 phosphate: role of nitric oxide)

IT 10102-43-9, Nitric oxide, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(determinants of anti-vascular action by **combretastatin**
A-4 phosphate: role of nitric oxide)

RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD

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IT 168555-66-6

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

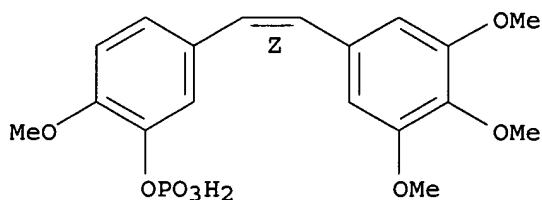
(determinants of anti-vascular action by **combretastatin**

A-4 phosphate: role of nitric oxide)

RN 168555-66-6 HCAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen phosphate, disodium salt (9CI) (CA INDEX NAME)

Double bond geometry as shown.



● 2 Na

L93 ANSWER 23 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
 AN 2000:592560 HCAPLUS
 DN 133:198575
 ED Entered STN: 25 Aug 2000
 TI Compositions and methods for use in **targeting vascular**
 destruction
 IN Pero, Ronald W.; Sherris, David
 PA **Oxigene, Inc., USA**
 SO PCT Int. Appl., 36 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 IC ICM A61K031-661
 ICS A61K031-6615; A61K031-664
 CC 63-5 (Pharmaceuticals)
 Section cross-reference(s): 1
 FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000048606	A1	20000824	WO 2000-US3996	20000216 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,				

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 CA 2358925 AA 20000824 CA 2000-2358925 20000216 <--
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 JP 2002537262 T2 20021105 JP 2000-599398 20000216 <--
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 AU 776511 B2 20040909 AU 2000-35973 20000216 <--
 EP 1547603 A2 20050629 EP 2004-76582 20000216 <--
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
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 US 2003109500 A1 20030612 US 2002-218833 20020814 <--
 PRAI US 1999-120478P P 19990218 <--
 EP 2000-914606 A3 20000216 <--
 US 2000-505402 A1 20000216 <--
 WO 2000-US3996 W 20000216 <--

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2000048606	ICM	A61K031-661
	ICS	A61K031-6615; A61K031-664
US 6538038	NCL	514/731.000; 424/600.000; 424/602.000; 424/603.000; 424/604.000; 424/605.000; 424/606.000; 514/733.000 <--
US 2003109500	NCL	514/096.000; 514/657.000; 514/130.000; 549/005.000; 558/199.000; 564/428.000 <--

OS MARPAT 133:198575

AB Treatment of warm-blooded animals having a tumor or non-malignant hypervascularization, by administering a sufficient amount of a cytotoxic agent formulated into a phosphate prodrug form having substrate specificity for microvessel phosphatases, so that microvessels are destroyed preferentially over other normal tissues, because the less cytotoxic prodrug form is converted to the highly cytotoxic dephosphorylated form.

ST antitumor prodrug microvessel phosphatase activation

IT Tubulins

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(-binding agents; prodrugs for use in **targeting**
vascular destruction)

IT Peptides, biological studies

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(cyclic, Dolastatins; prodrugs for use in **targeting**
vascular destruction)

IT Angiogenesis

(disorder; prodrugs for use in **targeting** **vascular**
 destruction)

IT Blood vessel

(microvessel; prodrugs for use in **targeting** **vascular**
 destruction)

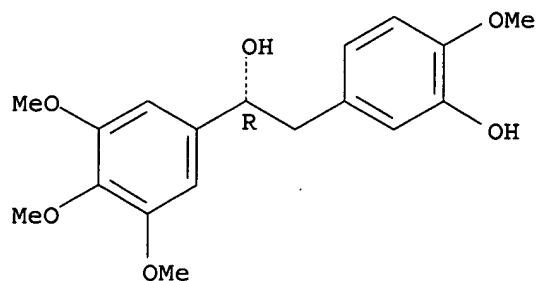
IT Angiogenesis inhibitors

Antitumor agents

(prodrugs for use in **targeting** **vascular**
 destruction)

- IT Flavonoids
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(prodrugs for use in **targeting vascular** destruction)
- IT Phosphates, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(prodrugs for use in **targeting vascular** destruction)
- IT Drug delivery systems
(prodrugs; prodrugs for use in **targeting vascular** destruction)
- IT Alkaloids, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(vinca; prodrugs for use in **targeting vascular** destruction)
- IT 64-86-8D, Colchicine, analogs 95-15-8D, Benzo[b]thiophene, derivs. 120-72-9D, Indole, derivs. 271-89-6D, Benzofuran, derivs. 362-07-2, 2-Methoxyestradiol 518-28-5D, Podophyllotoxin, derivs. 588-59-0D, Stilbene, derivs. 1605-68-1D, Taxane, derivs. 4765-58-6D, derivs. 41451-68-7D, Steganacin, derivs. 67346-69-4D, 1,8-Naphthyridin-4(1H)-one, aryl derivs. **82855-09-2, Combretastatin** 90996-54-6D, Rhizoxin, derivs. 91531-98-5D, Amphetamine, derivs. **109971-63-3** 136638-72-7D, derivs. 152044-53-6, Epothilone A 152044-54-7, Epothilone b 155233-30-0D, Curacin A, derivs. 159934-04-0D, Welwistatin, derivs. **168555-66-6** 179342-29-1 203448-32-2D, Phenstatin, derivs. **222030-63-9, Combretastatin 288847-34-7** 288847-36-9 288847-37-0 288847-38-1 288847-39-2 288847-40-5 288847-41-6 288847-42-7 288847-43-8
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(prodrugs for use in **targeting vascular** destruction)
- RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
- (1) Dark; Cancer Research 1997, V57(10), P1829 HCAPLUS
- IT **82855-09-2, Combretastatin 109971-63-3**
168555-66-6 222030-63-9, Combretastatin
288847-34-7
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(prodrugs for use in **targeting vascular** destruction)
- RN 82855-09-2 HCAPLUS
- CN Benzeneethanol, 3-hydroxy-4-methoxy- α -(3,4,5-trimethoxyphenyl)-, (α R)- (9CI) (CA INDEX NAME)

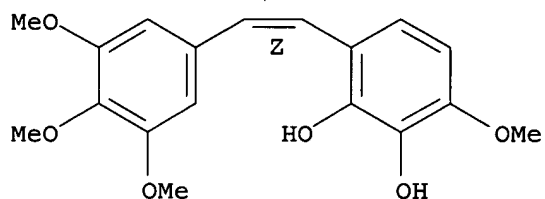
Absolute stereochemistry.



RN 109971-63-3 HCAPLUS

CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-
(9CI) (CA INDEX NAME)

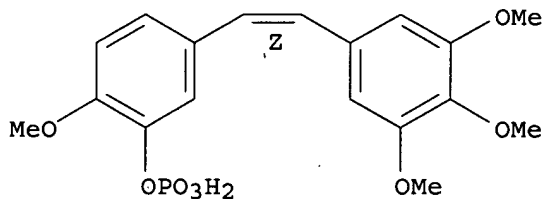
Double bond geometry as shown.



RN 168555-66-6 HCAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen
phosphate, disodium salt (9CI) (CA INDEX NAME)

Double bond geometry as shown.

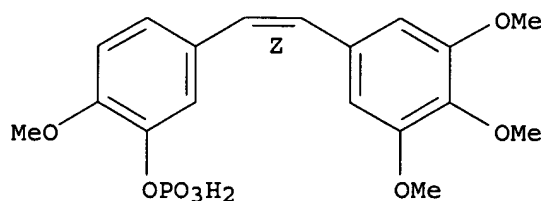


● 2 Na

RN 222030-63-9 HCAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen
phosphate (9CI) (CA INDEX NAME)

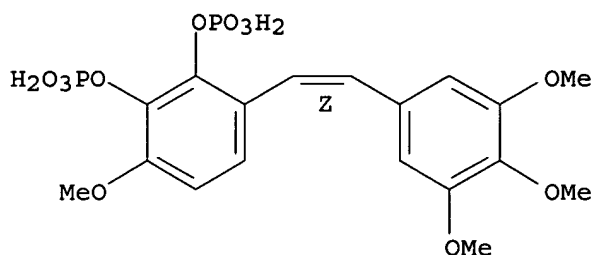
Double bond geometry as shown.



RN 288847-34-7 HCAPLUS

CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, bis(dihydrogen phosphate), tetrasodium salt (9CI) (CA INDEX NAME)

Double bond geometry as shown.



● 4 Na

L93 ANSWER 24 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 1999:762743 HCAPLUS

DN 132:44340

ED Entered STN: 03 Dec 1999

TI Pulmonary vascular gene transfer. Prospects for successful therapy of pulmonary hypertension

AU Fouty, Brian; Rodman, David M.

CS University of Colorado Health Sciences Center, Denver, CO, 80262, USA

SO American Journal of Respiratory Cell and Molecular Biology (1999), 21(5), 555-557

CODEN: AJRBEL; ISSN: 1044-1549

PB American Lung Association

DT Journal; General Review

LA English

CC 1-0 (Pharmacology)

AB A review with 8 refs. Successful application of gene-transfer technol. to the pulmonary circulation requires that the following four challenges be met: (1) identification of appropriate therapeutic genes, (2) improved vector efficiency, (3) specific pulmonary **vascular targeting**, and (4) elimination of the host-immune response to the vector and transgene. Gene therapy should provide an excellent opportunity to develop novel strategies for the therapy of pulmonary vascular disease.

ST review pulmonary vascular gene transfer hypertension therapy

IT **Antihypertensives**

Blood vessel

Gene therapy

(pulmonary vascular gene transfer and prospects for successful therapy

of pulmonary hypertension)
 IT Circulation
 Hypertension
 (pulmonary; pulmonary vascular gene transfer and prospects for
 successful therapy of pulmonary hypertension)
 RE.CNT 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD
 RE
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 L93 ANSWER 25 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
 AN 1999:449666 HCAPLUS
 DN 132:90067
 ED Entered STN: 22 Jul 1999
 TI Examples of adjuvant treatment enhancing the antitumor effect of
 photodynamic therapy
 AU Korbelik, Mladen; Cecic, Ivana; Sun, Jinghai; **Chaplin, David J.**
 CS British Columbia Cancer Agency, Vancouver, BC, Can.
 SO Proceedings of SPIE-The International Society for Optical Engineering (1999), 3592(Optical Methods for Tumor Treatment and Detection: Mechanisms and Techniques in Photodynamic Therapy VIII), 65-72
 CODEN: PSISDG; ISSN: 0277-786X
 PB SPIE-The International Society for Optical Engineering
 DT Journal; General Review
 LA English
 CC 8-0 (Radiation Biochemistry)
 Section cross-reference(s): 1, 15
 AB A review with 51 refs. Strategies for improving the clin. efficacy of photodynamic therapy (PDT) in treatment of solid cancers include applications of different types of adjuvant treatments in addition to this modality that may result in superior therapeutic outcome. Examples of such an approach investigated using mouse tumor models are presented in this report. It is shown that the cures of PDT treated s.c. tumors can be substantially improved by adjuvant therapy with: metoclopramide (enhancement of cancer cell apoptosis), **combretastatin A -4** (selective destruction of tumor neovasculature), Roussin's Black Salt (light activated tumor localized release of nitric oxide), or dendritic cell-based adoptive immunotherapy (immune rejection of treated tumor).
 ST review antitumor photodynamic therapy adjuvant
 IT Antitumor agents
 Immunotherapy
 Photodynamic therapy
 Photosensitizers (pharmaceutical)
 (adjuvant treatment enhancing antitumor effect of photodynamic therapy)
 IT 364-62-5, Metoclopramide 37305-51-4, Roussin Black Salt
117048-59-6, Combretastatin A-4
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(adjuvant treatment enhancing antitumor effect of photodynamic therapy)

RE.CNT 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD

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IT 117048-59-6, Combretastatin A-4

RL: BAC (Biological activity or effector, except adverse); BSU (Biological

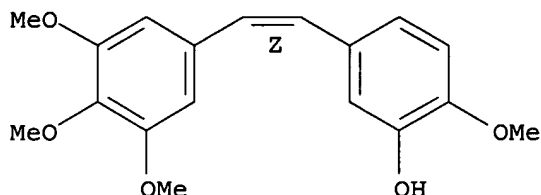
study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(adjuvant treatment enhancing antitumor effect of photodynamic therapy)

RN 117048-59-6 HCAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L93 ANSWER 26 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 1999:298062 HCAPLUS

DN 131:111003

ED Entered STN: 14 May 1999

TI Anti-vascular approaches to solid tumor therapy: evaluation of **combretastatin A4 phosphate**

AU Chaplin, D. J.; Pettit, G. R.; Hill, S. A.

CS Tumour Microcirculation Group, Gray Laboratory Cancer Research Trust, Mount Vernon Hospital, Northwood, Middlesex, UK

SO Anticancer Research (1999), 19(1A), 189-196

CODEN: ANTRD4; ISSN: 0250-7005

PB International Institute of Anticancer Research

DT Journal

LA English

CC 1-6 (Pharmacology)

AB **Combretastatin A4 phosphate** has recently been identified by us as an agent which can selectively damage tumor neovasculature. In the current study we establish that **combretastatin** induces extensive blood flow shutdown in the tumor compared to normal tissues. Histol. assessment of **vascular** shutdown shows that over 90% of vessels are rendered non-functional 6 h post-treatment with 100 mg/kg **i.p.** Measurement of blood flow using a diffusible tracer $^{86}\text{RbCl}$ indicates an overall reduction in perfusion by only 50-60%. This discrepancy probably reflects increased blood flow in the normal tissue vasculature supplying the tumor rim, which is caused by the ischemia-induced release of vasoactive mediators. The **vascular** shutdown induced by administration of 100 mg/kg of **combretastatin A4 phosphate** results in extensive cell loss in the 24 h following treatment, however this is not translated into any significant effect on tumor growth. The continued growth of the tumor is attributed to an actively proliferating population of cells at the periphery of the tumor, which are dependent on normal tissue vasculature for their survival. We have attempted to **target** this residual population by combining **combretastatin A4 phosphate** with cytotoxic approaches. Cis platinum and radiation have been used. The results show that **combretastatin** can significantly enhance tumor response to both cis platinum and radiation. In summary, the studies confirm **combretastatin A4 phosphate** as a novel agent which **targets** and damages tumor vasculature and, moreover, indicate its potential therapeutic usefulness as an adjuvant to conventional cytotoxic approaches.

ST antitumor neovascularization **combretastatin A4 phosphate**

IT Antitumor agents
(evaluation of **combretastatin A4 phosphate**
as anti-vascular approach to solid tumor therapy)

IT Angiogenesis
(neovascularization; evaluation of **combretastatin A4 phosphate** as anti-vascular approach to solid tumor therapy)

IT **168555-66-6, Combretastatin A4 disodium phosphate**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(evaluation of **combretastatin A4 phosphate**
as anti-vascular approach to solid tumor therapy)

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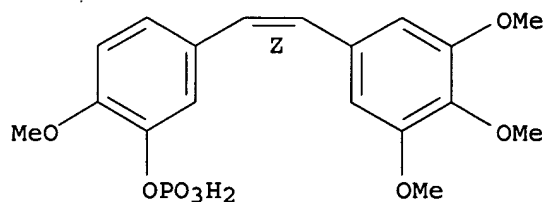
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IT **168555-66-6, Combretastatin A4 disodium phosphate**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(evaluation of **combretastatin A4 phosphate**
as anti-vascular approach to solid tumor therapy)

RN **168555-66-6** HCAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen phosphate, disodium salt (9CI) (CA INDEX NAME)

Double bond geometry as shown.



● 2 Na

L93 ANSWER 27 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 1999:241795 HCAPLUS

DN 131:39356

ED Entered STN: 20 Apr 1999

TI **Combretastatin A-4 phosphate** as a tumor **vascular-targeting** agent: early effects in tumors and normal tissues

AU Tozer, Gillian M.; Prise, Vivien E.; Wilson, John; Locke, Rosalind J.; Vojnovic, Borivoj; Stratford, Michael R. L.; Dennis, Madeleine F.; Chaplin, David J.

CS Tumor Microcirculation Group, Gray Laboratory, Cancer Research Trust, Mount Vernon Hospital, Northwood, HA6 2JR, UK

SO Cancer Research (1999), 59(7), 1626-1634

CODEN: CNREA8; ISSN: 0008-5472

PB AACR Subscription Office

DT Journal

LA English

CC 1-6 (Pharmacology)

AB The potential for tumor **vascular-targeting** by using the tubulin destabilizing agent disodium **combretastatin**

A-4 3-O-phosphate (CA-4-P) was assessed in a rat system. This approach aims to shut down the established tumor vasculature, leading to the development of extensive tumor cell necrosis. The early **vascular** effects of CA-4-P were assessed in the s.c. implanted P22 carcinosarcoma and in a range of normal tissues. Blood flow was measured by the uptake of radiolabeled iodoantipyrine, and quant. autoradiog. was used to measure spatial heterogeneity of blood flow in tumor sections. CA-4-P (100 mg/kg i.p.) caused a significant increase in mean arterial blood pressure at 1 and 6 h after treatment and a very large decrease in tumor blood flow, which-by 6 h-was reduced approx. 100-fold. The spleen was the most affected normal tissue with a 7-fold reduction in blood flow at 6 h. Calcns. of **vascular** resistance revealed some **vascular** changes in the heart and kidney for which there were no significant changes in blood flow. Quant. autoradiog. showed that CA-4-P increased the spatial heterogeneity in tumor blood flow. The drug affected peripheral tumor regions less than central regions. Administration of CA-4-P (30 mg/kg) in the presence of the nitric oxide synthase inhibitor, N ω -nitro-L-arginine Me ester, potentiated the effect of CA-4-P in tumor tissue. The combination increased tumor **vascular** resistance 300-fold compared with less than 7-fold for any of the normal tissues. This shows that tissue production of nitric oxide protects against the damaging **vascular** effects of CA-4-P. Significant changes in tumor **vascular** resistance could also be obtained in isolated tumor perfusions using a cell-free perfusate,

although the changes were much less than those observed in vivo. This shows that the action of CA-4-P includes mechanisms other than those involving red cell viscosity, intravascular coagulation, and neutrophil adhesion.

The uptake of CA-4-P and **combretastatin A-4**

(CA-4) was more efficient in tumor than in skeletal muscle tissue and dephosphorylation of CA-4-P to CA-4 was faster in the former. These results are promising for the use of CA-4-P as a tumor **vascular-targeting** agent.

ST antitumor antiangiogenic **combretastatin A4 phosphate** NO

IT Angiogenesis inhibitors

Antitumor agents

Blood vessel

Circulation

(**combretastatin A-4 phosphate**

as a tumor **vascular-targeting** agent)

IT 117048-59-6, **Combretastatin A-4**

168555-66-6

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(**combretastatin A-4 phosphate**

as a tumor **vascular-targeting** agent)

IT 50903-99-6, N ω -Nitro-L-arginine methyl ester

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(**combretastatin A-4 phosphate**

as a tumor **vascular-targeting** agent)

IT 10102-43-9, Nitric oxide, biological studies

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(**combretastatin A-4 phosphate**

as a tumor **vascular-targeting** agent)

RE.CNT 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD

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IT 117048-59-6, Combretastatin A-4

168555-66-6

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

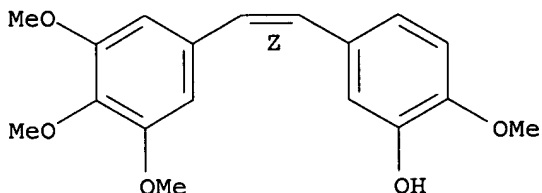
(combretastatin A-4 phosphate

as a tumor vascular-targeting agent)

RN 117048-59-6 HCAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

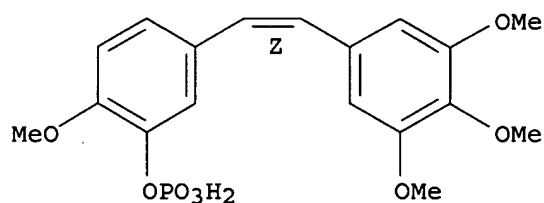
Double bond geometry as shown.



RN 168555-66-6 HCAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen phosphate, disodium salt (9CI) (CA INDEX NAME)

Double bond geometry as shown.



● 2 Na

L93 ANSWER 28 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
 AN 1998:404526 HCAPLUS
 DN 129:172497
 ED Entered STN: 02 Jul 1998
 TI Magnetic resonance imaging and spectroscopy of **combretastatin A4** prodrug-induced disruption of tumor perfusion and energetic status
 AU Beauregard, D. A.; Thelwall, P. E.; Chaplin, D. J.; Hill, S. A.; Adams, G. E.; Brindle, K. M.
 CS Department of Biochemistry, University of Cambridge, Cambridge, CB2 1GA, UK
 SO British Journal of Cancer (1998), 77(11), 1761-1767
 CODEN: BJCAAI; ISSN: 0007-0920
 PB Churchill Livingstone
 DT Journal
 LA English
 CC 8-9 (Radiation Biochemistry)
 Section cross-reference(s): 1
 AB The effects of **combretastatin A4** prodrug on perfusion and the levels of 31P metabolites in an implanted murine tumor were investigated for 3 h after drug treatment using NMR imaging (MRI) and spectroscopy (MRS). The area of regions of low signal intensity in spin-echo images of tumors increased slightly after treatment with the drug. These regions of low signal intensity corresponded to necrosis seen in histol. sections, whereas the expanding regions surrounding them corresponded to hemorrhage. Tumor perfusion was assessed before and 160 min after drug treatment using dynamic MRI measurements of gadolinium diethylenetriaminepentaacetate (Gd DTPA) uptake and washout. Perfusion decreased significantly in central regions of the tumor after treatment. This was attributed to disruption of the vasculature and was consistent with the hemorrhage seen in histol. sections. The mean apparent diffusion coefficient of water within the tumor did not change, indicating that there was no expansion of necrotic regions during the 3 h after drug treatment. Localized 31P-MRS showed that there was decline in cellular energy status in the tumor after treatment with the drug. The concns. of nucleoside **triphosphates** within the tumor fell, the inorg. **phosphate** concentration increased and there was a significant decrease in tumor pH for 80 min after drug treatment. The rapid, selective and extensive damage caused to these tumors by **combretastatin A4** prodrug has highlighted the potential of the agent as a novel cancer chemotherapeutic agent. We have shown that the response of tumors to treatment with the drug may be monitored non-invasively using MRI and MRS expts. that are appropriate for use in a clin. setting.
 ST GdDTPA MRI tumor perfusion **combretastatin A4**
 IT Imaging

(NMR; magnetic resonance imaging and spectroscopy of **combretastatin A4** prodrug-induced disruption of tumor perfusion and energetic status)

IT Neoplasm
Perfusion
(magnetic resonance imaging and spectroscopy of **combretastatin A4** prodrug-induced disruption of tumor perfusion and energetic status)

IT 20694-16-0
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(magnetic resonance imaging and spectroscopy of **combretastatin A4** prodrug-induced disruption of tumor perfusion and energetic status)

IT 117048-59-6, **Combretastatin A4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(magnetic resonance imaging and spectroscopy of **combretastatin A4** prodrug-induced disruption of tumor perfusion and energetic status)

RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

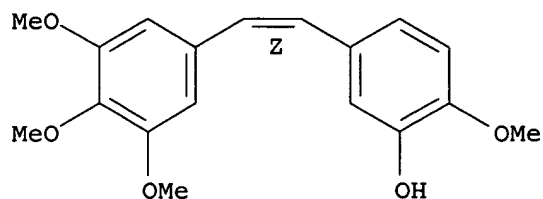
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IT 117048-59-6, **Combretastatin A4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(magnetic resonance imaging and spectroscopy of **combretastatin A4** prodrug-induced disruption of tumor perfusion and energetic status)

RN 117048-59-6 HCAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L93 ANSWER 29 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN
 AN 1997:198361 HCAPLUS
 DN 126:258604
 ED Entered STN: 27 Mar 1997
 TI Effects of novel and conventional anti-cancer agents on human endothelial permeability: influence of tumor secreted factors
 AU Watts, Margaret E.; Woodcock, Michael; Arnold, Stephanie; Chaplin, David J.
 CS Tumor Microcirculation Group, Gray Lab. Cancer Res. Trust, Middlesex, HA6 2JR, UK
 SO Anticancer Research (1997), 17(1A), 71-75
 CODEN: ANTRD4; ISSN: 0250-7005
 PB Anticancer Research
 DT Journal
 LA English
 CC 1-6 (Pharmacology)
 AB A number of anti-cancer agents have been implicated in vascular toxicity. The effects have been attributed to direct drug toxicity towards endothelium. Little attention has been focused on the interaction between anticancer drugs, endothelial cells and tumor secreted factors. It is well known that tumors can secrete factors such as vascular permeability factor which do affect endothelial cells and could alter their response to the vascular effects of anticancer drugs. In the present study, we have examined, in vitro, the direct effects of vinblastine (VBL), 5-fluorouracil (5-FU), melphalan (L-PAM) and the novel tubulin inhibitor **combretastatin A-1** (CBS) on endothelial permeability under normal and tumor simulated conditions. Monolayers of human umbilical vein endothelial cells (HUVEC) grown on membrane filters were incubated by the human melanoma cell line, RPMI-7951 (TCM). VBL caused rapid increase in permeability during the first 20 mins, which was maintained for the duration of the experiment (120 mins). The effect was not altered by TCM or restored to control levels when VBL was replaced by drug-free medium. Similarly, CBS caused a rapid increase in permeability; however, in contrast to VBL, this increase was enhanced by TCM. The changes induced by VBL and CBS were accompanied by contraction of the endothelial F-actin cytoskeleton. Neither L-PAM nor 5-FU altered the permeability of HUVEC monolayers. This study demonstrates that certain anti-cancer agents have a direct effect on endothelial cells, leading to an increase in the permeability of endothelial monolayers. Both VBL and CBS have vascular components in their mode of action which may lead to vascular collapse and tumor necrosis.

ST antitumor drug vascular endothelium permeability melanoma
 IT Blood vessel
 (endothelium, permeability; novel and conventional antitumor drug effect on human endothelial permeability: influence of tumor secreted factors)
 IT Antitumor agents
 (melanoma; novel and conventional antitumor drug effect on human endothelial permeability: influence of tumor secreted factors)

IT Antitumor agents
 (novel and conventional antitumor drug effect on human endothelial permeability: influence of tumor secreted factors)

IT 51-21-8, 5-Fluorouracil 148-82-3, Melphalan 865-21-4, Vinblastine 109971-63-3, **Combretastatin A-1**
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (novel and conventional antitumor drug effect on human endothelial permeability: influence of tumor secreted factors)

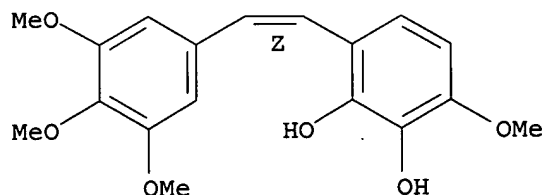
IT 127464-60-2, Vascular endothelial growth factor
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (novel and conventional antitumor drug effect on human endothelial permeability: influence of tumor secreted factors)

IT 109971-63-3, **Combretastatin A-1**
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (novel and conventional antitumor drug effect on human endothelial permeability: influence of tumor secreted factors)

RN 109971-63-3 HCAPLUS

CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



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FILE COVERS 1974 TO 30 Jun 2005 (20050630/ED)

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AN 2004400303 EMBASE

TI **Combretastatin A4 phosphate**: Background and current clinical status.

AU Young S.L.; Chaplin D.J.

CS S.L. Young, OXiGENE Inc., 230 Third Avenue, Waltham, MA 02451, United States. syoung@oxigene.com

SO Expert Opinion on Investigational Drugs, (2004) Vol. 13, No. 9, pp. 1171-1182.

Refs: 59
ISSN: 1354-3784 CODEN: EOIDER
CY United Kingdom
DT Journal; General Review
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy
LA English
SL English
ED Entered STN: 20041007
Last Updated on STN: 20041007
AB **Combretastatin A4 phosphate (CA4P)**
represents the lead compound in a group of novel tubulin depolymerising agents being developed as vascular targeting agents (VTAs). VTAs are drugs that induce rapid and selective vascular dysfunction in tumours. **CA4P** is a water-soluble prodrug of the cis-stilbene CA4 originally isolated from the tree *Combretum caffrum*. Preclinical studies have shown that **CA4P** induces blood flow reductions and subsequent tumour cell death in a variety of preclinical models. Moreover, this activity has been linked to its ability to rapidly alter the morphology of immature endothelial cells by disrupting their tubulin cytoskeleton. Phase I clinical trials have established a maximum tolerated dose in the range 60 - 68 mg/m² and in addition have established that significant changes to tumour perfusion can be achieved across a wide range of doses. The dose-limiting toxicities include tumour pain, ataxia and cardiovascular changes. The maximum tolerated dose was independent of schedule, indicating the absence of cumulative toxicity. Although unexpected from preclinical studies, some evidence of clinical response was seen using **CA4P** as a single modality. Based on the Phase I data, combination studies of **CA4P** with established therapies are in progress and should determine whether the exciting preclinical data obtained when VTAs are used in combination with cytotoxic chemotherapy, radiation, radioimmunotherapy and even antiangiogenic agents, can be translated into man. 2004 .COPYRG. Ashley Publications Ltd.
CT Medical Descriptors:
Combretum
cancer combination chemotherapy
cancer radiotherapy
radioimmunotherapy
drug targeting
drug selectivity
drug solubility
drug cytotoxicity
drug synthesis
drug formulation
drug storage
drug protein binding
drug potency
drug sensitivity
drug potentiation
drug megadose
drug safety
drug efficacy
drug tolerability
drug blood level
drug urine level
drug half life
drug accumulation

drug clearance
drug excretion
single drug dose
antineoplastic activity
structure activity relation
maximum tolerated dose
area under the curve
distribution volume
low drug dose
pain: SI, side effect
ataxia: SI, side effect
cardiovascular disease: SI, side effect
powder
dyspnea: SI, side effect
ischemic heart disease: SI, side effect
neurologic disease: SI, side effect
hematologic malignancy: DT, drug therapy
thyroid carcinoma: DT, drug therapy
head and neck tumor: DT, drug therapy
prostate cancer: DT, drug therapy
lung non small cell cancer: DT, drug therapy
ovary carcinoma: DT, drug therapy
colorectal carcinoma: DT, drug therapy
chemotherapy induced emesis: SI, side effect
headache: SI, side effect
fatigue: SI, side effect
blood toxicity: SI, side effect
stomatitis: SI, side effect
alopecia: SI, side effect
gastrointestinal symptom: SI, side effect
diarrhea: SI, side effect
abdominal pain: SI, side effect
paresthesia: SI, side effect
skin tingling: SI, side effect
visual impairment: SI, side effect
diplopia: SI, side effect
muscle weakness: SI, side effect
cardiotoxicity: SI, side effect
heart arrhythmia: SI, side effect
QT prolongation: SI, side effect
tachycardia: SI, side effect
bradycardia: SI, side effect
hypertension: DT, drug therapy
hypertension: SI, side effect
hypoxia: SI, side effect
ovary cancer: DT, drug therapy
heart infarction: SI, side effect
stridor: SI, side effect
apnea: SI, side effect
syncope: SI, side effect
intestine ischemia: SI, side effect
drug fatality: SI, side effect
dehydration: SI, side effect
heart ventricle arrhythmia: SI, side effect
neck pain: DT, drug therapy
neck pain: SI, side effect
lethargy: SI, side effect
sinus tachycardia: SI, side effect
dizziness: SI, side effect
respiration depression: DT, drug therapy

respiration depression: SI, side effect
 pulmonary hypertension: SI, side effect
 heart output
 heart ventricle extrasystole: SI, side effect
 ST segment depression
 PR interval
 QT interval
 QRS complex
 T wave
 ECG abnormality: SI, side effect
 kidney cancer: DT, drug therapy
 bone marrow suppression: SI, side effect
 human
 nonhuman
 clinical trial
 review

Drug Descriptors:

*combretastatin A4 phosphate: AE, adverse drug reaction
 *combretastatin A4 phosphate: CT, clinical trial
 *combretastatin A4 phosphate: AD, drug administration
 *combretastatin A4 phosphate: AN, drug analysis
 *combretastatin A4 phosphate: CB, drug combination
 *combretastatin A4 phosphate: CM, drug comparison
 *combretastatin A4 phosphate: CR, drug concentration
 *combretastatin A4 phosphate: DV, drug development
 *combretastatin A4 phosphate: DO, drug dose
 *combretastatin A4 phosphate: IT, drug interaction
 *combretastatin A4 phosphate: DT, drug therapy
 *combretastatin A4 phosphate: PR, pharmaceuticals
 *combretastatin A4 phosphate: PK, pharmacokinetics
 *combretastatin A4 phosphate: PD, pharmacology
 *combretastatin A4 phosphate: IV, intravenous drug administration

tubulin: EC, endogenous compound

colchicine: AE, adverse drug reaction

CT Drug Descriptors:

colchicine: CM, drug comparison
 cisplatin: CT, clinical trial
 cisplatin: CB, drug combination
 cisplatin: IT, drug interaction
 cisplatin: DT, drug therapy
 cyclophosphamide: CB, drug combination
 cyclophosphamide: IT, drug interaction
 fluorouracil: CB, drug combination
 fluorouracil: IT, drug interaction
 doxorubicin: CT, clinical trial
 doxorubicin: CB, drug combination
 doxorubicin: IT, drug interaction
 doxorubicin: DT, drug therapy
 chlorambucil: CB, drug combination
 chlorambucil: IT, drug interaction
 melphalan: CB, drug combination
 melphalan: IT, drug interaction
 irinotecan: CB, drug combination
 irinotecan: IT, drug interaction
 paclitaxel: CT, clinical trial
 paclitaxel: CB, drug combination
 paclitaxel: IT, drug interaction
 paclitaxel: DT, drug therapy
 carboplatin: CT, clinical trial
 carboplatin: CB, drug combination

carboplatin: DT, drug therapy
 gadolinium pentetate
 Vinca alkaloid: AE, adverse drug reaction
 Vinca alkaloid: CM, drug comparison
 taxane derivative: AE, adverse drug reaction
 taxane derivative: CM, drug comparison
 hydromorphone: AE, adverse drug reaction
 hydromorphone: DT, drug therapy
 lorazepam: DT, drug therapy
 naloxone: DT, drug therapy
 benazepril plus hydrochlorothiazide: DT, drug therapy
 metoprolol succinate: DT, drug therapy
 nitroprusside sodium: DT, drug therapy
propranolol: DT, drug therapy

dilaudid cr

benazepril

RN (combretastatin A4 phosphate)

168555-66-6, 222030-63-9; (colchicine) 64-86-8;
 (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2; (cyclophosphamide)
 50-18-0; (fluorouracil) 51-21-8; (doxorubicin) 23214-92-8, 25316-40-9;
 (chlorambucil) 305-03-3; (melphalan) 148-82-3; (irinotecan) 100286-90-6;
 (paclitaxel) 33069-62-4; (carboplatin) 41575-94-4; (gadolinium pentetate)
 80529-93-7; (hydromorphone) 466-99-9, 71-68-1; (lorazepam) 846-49-1;
 (naloxone) 357-08-4, 465-65-6; (metoprolol succinate) 98418-47-4;
 (nitroprusside sodium) 14402-89-2, 15078-28-1; (
propranolol) 13013-17-7, 318-98-9,
3506-09-0, 4199-09-1, 525-66-6; (benazepril)
 86541-75-5

CN Cpt 11; Dilaudid cr; Ativan; Narcan; Lotensin; Toprol xl

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(FILE 'HOME' ENTERED AT 14:07:47 ON 05 JUL 2005)
 SET COST OFF

FILE 'HCAPLUS' ENTERED AT 14:07:56 ON 05 JUL 2005

E CHAPLIN D/AU
 L1 364 S E3-E9,E11-E18
 E YOUNG S/AU
 L2 622 S E3-E30
 E YOUNG SCOT/AU
 L3 61 S E4-E14
 E OXIGENE/PA,CS
 L4 18 S E3-E10
 L5 511 S ?COMBRETASTATIN?
 L6 370 S ?COMBRETASTATIN?() (A1 OR A4 OR A 1 OR A 4)
 L7 129 S L6(L)?PHOSPHATE?
 L8 8 S L7 AND A1

FILE 'REGISTRY' ENTERED AT 14:12:12 ON 05 JUL 2005

L9 1 S 82855-09-2
 L10 283 S C18H22O6/MF AND 46.150.18/RID AND 2/NR
 L11 8 S L10 AND BENZENEETHANOL
 L12 3 S L11 AND 3 4 5 TRIMETHOXYPHENYL
 L13 2 S L12 NOT 4 HYDROXY
 L14 5 S L10 AND COMBRETASTATIN
 L15 5 S L9,L13,L14
 L16 2 S 117048-59-6 OR 109971-63-3

jan delaval - 5 july 2005

L17 609 S C18H20O5/MF AND 46.150.18/RID AND 2/NR
L18 4 S L17 AND COMBRETASTATIN
L19 16 S L17 AND PHENOL AND ETHENYL
L20 3 S L19 AND 3 4 5 TRIMETHOXYPHENYL ETHENYL AND 2 METHOXY 5
L21 5 S L18,L20
L22 311 S C18H20O6/MF AND 46.150.18/RID AND 2/NR
L23 1 S L22 AND COMBRETASTATIN
L24 3 S L22 AND 1 2 BENZENEDIOL AND 3 4 5 TRIMETHOXYPHENYL ETHENYL AN
L25 2 S 222030-63-9 OR 288847-35-8
L26 5 S C18H21O8P/MF AND 46.150.18/RID AND 2/NR
L27 3 S L26 AND ETHENYL
L28 3 S C18H22O12P2/MF AND 46.150.18/RID AND 2/NR AND ETHENYL
L29 19 S L9,L15,L16,L21,L23,L24,L25,L27,L28
E COMBRETASTATIN
L30 33 S E3
L31 11 S L30 AND L29
L32 19 S L29,L31
L33 22 S L30 NOT L32
L34 41 S L32,L33
SEL RN
L35 51 S E1-E41/CRN
L36 25 S L35 AND (COMPD OR WITH OR MXS/CI)
L37 26 S L35 NOT L36
L38 64 S L34,L37

FILE 'HCAPLUS' ENTERED AT 14:23:14 ON 05 JUL 2005

L39 394 S L38
L40 511 S L5-L8
L41 52 S CA4P OR CA 4P
L42 540 S L39-L41
L43 1418 S PROPRANOLOL
L44 9563 S (NA OR SODIUM) () (NITROPRUSSIDE OR NITRO PRUSSIDE)

FILE 'REGISTRY' ENTERED AT 14:25:34 ON 05 JUL 2005

L45 2 S 5051-22-9 OR 4199-09-1
E C16H21NO2/MF
L46 29 S E3 AND C6-C6/ES AND 2/NR AND 2 PROPRANOL
L47 12 S L46 AND 3 1 NAPHTHALENYLOXY
L48 3 S L47 NOT (D/ELS OR 180 OR T/ELS OR 11C# OR 13C# OR LABELED)
L49 3 S E3 AND PROPRANOLOL
L50 3 S L45,L48,L49
SEL RN
L51 121 S E1-E3/CRN
L52 17 S L51 NOT (MXS/CI OR COMPD OR WITH)
L53 16 S L52 NOT CONJUGATE
L54 19 S L50,L53
L55 1 S 14402-89-2
L56 1 S 15078-28-1
L57 480 S 15078-28-1/CRN
L58 30 S L57 AND NA/ELS
L59 5 S L58 AND 2/NC
SEL RN 4 5
L60 2 S E4-E5
L61 3 S L56,L60,L55

FILE 'HCAPLUS' ENTERED AT 14:30:02 ON 05 JUL 2005

L62 15018 S L54
L63 27374 S PROPRANOLOL
L64 4507 S L61
L65 40302 S L43,L44,L62-L64

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      E BETA BLOCKER/CT
      E E4+ALL
      E E2+ALL
L109      63550 S E14+NT
      E ANTIHYPERTEN/CT
L110      177019 S E5+NT
L111      1005 S L105 AND L106-L110
L112      2 S L111 AND L102,L103
L113      52 S L111 AND L43,L44
L114      0 S L113 AND L112
L115      259 S VASCULAR? TARGET?
      E ANTINEOPLASTIC/CT
L116      597399 S E7+NT
      E STILBENES/CT
      E E3+ALL
L117      27719 S E8+NT
L118      19169 S L116 AND L117
L119      1589 S L116 AND L105
L120      149 S L118,L119 AND L106-L110
L121      135 S L120 AND L117
L122      119 S L121 AND PY<=2002
L123      27774 S L102 OR L103 OR L117
L124      212 S L123 AND L109,L110
L125      67 S L123 AND L106-L108
L126      235 S L124,L125
L127      213 S L126 AND PY<=2002
L128      50 S L127 NOT AB/FA
L129      163 S L127 NOT L128
L130      157 S L129/ENG
L131      6 S L129 NOT L130
L132      19 S L130 AND C4./CT
L133      138 S L130 NOT L132
L134      278 S L104,L115 AND L106-L108
L135      148 S L104,L115 AND L109
L136      850 S L104,L115 AND L110
L137      703 S L134-L136 AND PY<=2002
L138      8 S L137 AND C4./CT

FILE 'EMBASE' ENTERED AT 15:03:38 ON 05 JUL 2005
L139      434 S L5-L8 OR L41 OR L38
L140      434 S ?COMBRETASTATIN?
L141      434 S L139,L140
L142      25 S COMBRESTATIN?
L143      447 S L141,L142
L144      76898 S L43 OR L44 OR L63
L145      80486 S L54 OR L61
L146      2 S L144,L145 AND L143
L147      1 S L146 AND ?COMBRETASTATIN?/TI

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FILE 'EMBASE' ENTERED AT 15:07:07 ON 05 JUL 2005

FILE 'EMBASE' ENTERED AT 15:07:55 ON 05 JUL 2005

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Creation date: 09-28-2005
Indexing Officer: LCHEO - LEE CHEO
Team: OIPEBackFileIndexing
Dossier: 10321784

Legal Date: 09-27-2005

No.	Doccode	Number of pages
1	CTNF	17
2	892	1
3	NPL	8
4	FWCLM	1
5	SRFW	1

Total number of pages: 28

Remarks:

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